

VOLUME 9 - PHARMACOVIGILANCE

Medicinal Products for Human use and Veterinary Medicinal Products

FOREWORD

Directive 2001/83/EC and Directive 2001/82/EC specifically requires the European Commission in consultation with the European Agency for the Evaluation of Medicinal Products (the Agency), Member States and interested parties to draw up guidance on the collection, verification and presentation of adverse reaction reports in order to facilitate the exchange of information about pharmacovigilance within the Community. Articles 24 and 46 of Council Regulation (EEC) No. 2309/93 includes the same requirement.

This guidance is required to include technical requirements for the electronic exchange of pharmacovigilance information in accordance with internationally agreed formats. In addition, the Commission is also required to publish a reference to an internationally agreed medical terminology. This guidance shall be published in Volume 9 of *The rules governing medicinal products in the European Union*.

This present volume has thus been prepared by the European Commission in close consultation with the Agency, Member States and interested parties and is specifically related to pharmacovigilance. It brings together general guidance on the requirements, procedures, roles and activities in this field, for both Marketing Authorisation Holders and Competent Authorities of medicinal products for human use and veterinary medicinal products; it incorporates international agreements reached within the framework of the International Conference on Harmonisation (ICH) or the Veterinary International Conference on Harmonisation (VICH).

Volume 9 is presented in four parts:

Part I deals with pharmacovigilance of medicinal products for human use.

Part II addresses pharmacovigilance of veterinary medicinal products

Part III provides general information on EU electronic exchange of pharmacovigilance data.

Part IV provides general reference to administrative and legislative information relevant to both medicinal products for human use and veterinary medicinal products.

*It should be noted, as with all guidance documents in rapidly evolving legislative and technical areas, that this guidance is intended to be regularly reviewed and updated. It is anticipated that further updates will be published on the European Commission website:
<http://pharmacos.eudra.org/F2/eudralex/index.htm>.*

It should also be noted that the terms “drug” and “medicinal product” are considered as synonyms for the purposes of the guidance in this volume.

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PART I - MEDICINAL PRODUCTS FOR HUMAN USE

1. Guidance and Procedures for Marketing Authorisation Holders

1.1 Legal Basis and Purpose

The legal framework for pharmacovigilance of medicinal products for human use in the Community is given in Council Regulation (EEC) No 2309/93 (Title II, Chapter 3), Commission Regulation (EC) No 540/95 and Council Directive 2001/83/EC - The requirements explained in these guidelines are based on the ICH guidelines, where these exist, but may be further specified or contain additional requests in line with the legislation of the Community.

Pharmacovigilance activities come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the medicinal product under normal conditions of use in the marketing situation. Pharmacovigilance obligations apply to all authorised medicinal products including those authorised before 1 January 1995.

Council Regulation (EEC) No 2309/93 (Title II, Chapter 3) and Council Directive -2001/83/EC as amended - describe the respective obligations of the marketing authorisation holder and of the competent authorities to set up a system for pharmacovigilance in order to collect, collate and evaluate information about suspected adverse reactions. All relevant information should be shared between the competent authorities and the marketing authorisation holder, in order to allow all parties involved in pharmacovigilance activities to assume their obligations and responsibilities. This requires an intensive exchange of information between the marketing authorisation holder, the Member States and the Agency as well as procedures to avoid duplication, maintain confidentiality and ensure the quality of the systems and data.

The EFTA states Iceland, Liechtenstein and Norway have through the Agreement of the European Economic Area (EEA) adopted the complete Community acquis on medicinal products, and are consequently parties to the Centralised Procedure and other community procedures. Consequently, the following guidance does not only apply with regard to the marketing authorisation holder obligations towards competent authorities in Member States of the European Union (EU) but also to those towards the EFTA States Iceland, Liechtenstein and Norway.

The obligations concerned with the monitoring of ADRs occurring in clinical trials with unauthorised products do not fall within the scope of pharmacovigilance activities, as described in these guidelines. The legal framework for such obligations is *Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provision of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*¹ or relevant national legislation until this new Directive is implemented, at the latest, from 1st May 2004.

1.1.1 Roles and responsibilities of marketing authorisation holders

The marketing authorisation holder must ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary.

The marketing authorisation holder should have permanently and continuously at its disposal, in the European Economic Area (EEA), a qualified person responsible for pharmacovigilance. This person should have experience in all aspects of pharmacovigilance and if not medically qualified should report to, or have access to a medically qualified person. The name of the qualified person responsible for pharmacovigilance should be provided to the competent authorities of the Member States, and for centrally authorised products to the Agency as well. National regulations in some Member States require a nominated individual in that country who has specific legal obligations in respect of

¹ OJ L 121 1.5.2001 p.34

pharmacovigilance at a national level. One such individual may also act as the qualified person responsible for pharmacovigilance for the European Union. Alternatively, the qualified person responsible for pharmacovigilance may be a separate person, additional to any required under the relevant national regulations. Thus, there must always be one qualified person responsible for pharmacovigilance at European Union level, but there may be a need for additional nominated individuals at a national level if products are authorised for marketing in Member States where this is required.

The responsibilities of the qualified person responsible for pharmacovigilance are as follows:

- the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the marketing authorisation holder, including to medical representatives, is collected and collated in order to be accessible at least at one point within the Community
- the preparation for competent authorities of the Member States, where the medicinal product is authorised, of the reports referred to in Article 104 of Council Directive 2001/83 - and in case of centrally authorised products the preparation for the Agency and competent authorities of the Member States of the reports referred to in Article 22 of Council Regulation (EEC) No 2309/93. Detailed guidance for the preparation of these reports are included in the following sections of this chapter:
 - adverse drug reaction (ADR) reports
 - Periodic Safety Update Reports (PSURs)
 - company sponsored post-authorisation study reports
- The marketing authorisation holder is also responsible for on-going pharmacovigilance evaluation during the post-authorisation period and for ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned.
- The provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation safety studies.

Marketing authorisation holders should therefore ensure that all information relevant to the balance of benefits and risks of a medicinal product is reported to the competent authorities fully and promptly, and also to the Agency in the case of centrally authorised products.

When marketing authorisation holders are involved in relationships including those that are contractual, arrangements for meeting pharmacovigilance obligations should be clearly specified in writing to the competent authority at the time the authorisation is granted, and subsequently when any changes to the arrangements are proposed.

When two or more separately authorised products, which are identical in all respects apart from their trade name, are marketed in the same territory by separate marketing authorisation holders, each marketing authorisation holder is obliged to meet the pharmacovigilance obligations described below. Where co-marketing arrangements exist, the marketing authorisation holders may enter into practical arrangements, in order to meet their obligations. Such arrangements must be notified in writing to the competent authorities when the authorisation is granted and subsequently when any changes to the arrangements are proposed. Such arrangements for joint pharmacovigilance data collection and

analyses are acceptable to the competent authorities, provided the marketing authorisation holder confirms in writing to the competent authority that it understands that legal responsibility in respect of pharmacovigilance rests with it.

Separate marketing authorisation holders may consider it appropriate to appoint the same person as qualified person responsible for pharmacovigilance for products where the above arrangements apply.

1.1.2 The competent authorities

1.1.2.1 The competent authorities of the Member States

The authorities of the Member States are the competent authorities for medicinal products authorised nationally through national procedures, including the mutual recognition procedure. The responsibilities for pharmacovigilance rest with the competent authorities of all the Member States in which the authorisations are held.

1.1.2.2 The European Commission

In the case of centrally authorised medicinal products the European Commission is the competent authority. The European Commission is responsible for the adoption of Decisions on the basis of CPMP Opinions relating to centrally authorised products and those products subject to the procedure of Articles 32 and 33 of Council Directive 2001/83/EC -

1.1.3 The role of the various parties in the EU pharmacovigilance system

1.1.3.1 The role of the competent authorities of the Member States for products authorised through national procedures

In accordance with the legislation, each Member State has established a pharmacovigilance system for the collection and evaluation of information relevant to the benefit to risk balance of medicinal products. The competent authority continually monitors the safety profile of the products available on its territory and takes appropriate action where necessary and monitors the compliance of marketing authorisation holders with their obligations with respect to pharmacovigilance.

1.1.3.2 The role of the reference Member State in the mutual recognition procedure

The responsibilities of pharmacovigilance rest with the competent authorities of all of the Member States in which the authorisations are held. For practical reasons, the Member States agree that the reference Member State will normally take the lead for medicinal products authorised through the mutual recognition procedure and responsibility for evaluating and producing assessment reports on pharmacovigilance issues related to that mutually recognised product, in accordance with an agreed timetable. The reference Member State takes responsibility for the co-ordination of communication with the marketing authorisation holder on such matters (see also Chapter 2.3 on *Conduct of Pharmacovigilance for Medicinal Products Authorised through the Mutual Recognition Procedure*) and for the monitoring of the compliance of the marketing authorisation holder with its obligations with respect to pharmacovigilance. These arrangements do not replace the legal responsibilities of the marketing authorisation holder with respect to individual competent authorities.

1.1.3.3 The role of the rapporteur in the centralised procedure

The competent authorities of the Member States are responsible for monitoring centrally authorised medicinal products in their respective territories. However, the pre-authorisation rapporteur takes the lead in pharmacovigilance, unless otherwise decided by the CPMP. The rapporteur is responsible for evaluating and producing assessment reports on pharmacovigilance issues related to a centrally authorised product, in accordance with an agreed timetable (see also Chapter 2.2 on *Conduct of*

Pharmacovigilance for Centrally Authorised Products) and for the monitoring of the compliance of the marketing authorisation holder with its obligations with respect to pharmacovigilance.

1.1.3.4 The role of the Agency in the centralised procedure

The role of the Agency secretariat is one of co-ordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure their safe and effective use, in particular by evaluating and making available through a database information on adverse reactions to the medicinal products in question (pharmacovigilance).

The Agency's scientific committee, the CPMP, aided by its Pharmacovigilance Working Party (PhVWP) is responsible for evaluating evidence and formulating Opinions on emerging drug safety issues with centrally authorised products, based on the rapporteur's assessment report. The Agency secretariat is responsible for communicating with the marketing authorisation holders of centrally authorised products on such issues (see also Chapter 2.2 on *Conduct of Pharmacovigilance for Centrally Authorised Products*) and for the co-ordination of issues relating to the monitoring of the compliance of the marketing authorisation holder with its pharmacovigilance obligations.

1.1.3.5 The role of the Agency in referrals of national and mutually recognised medicinal products

The role of the Agency secretariat is one of co-ordination in the case of referrals made to the CPMP for application of the procedure laid down in Articles 32 and 33 of Council Directive 2001/83/EC - - The different types of referrals are described in Chapter 3 of the *Notice to Applicants, Volume 2A* as updated in -November 2002 or subsequently². The CPMP, aided by its Pharmacovigilance Working Party (PhVWP), is responsible for evaluating evidence and formulating Opinions on matters referred to it.

1.1.3.6 The role of the Pharmacovigilance Working Party (PhVWP)

The principal mandate of the CPMP's Pharmacovigilance Working Party is to provide a forum of dialogue between Member States on pharmacovigilance and to review safety issues at the request of the competent authorities and for centrally authorised products and products referred under Article 32 and 33 of Council Directive 2001/83/EC - at the request of the CPMP in order to provide recommendations. -

1.1.4 Pharmacovigilance guidelines

In accordance with Article 24 of Council Regulation (EEC) No 2309/93 and Article 106 (1)-of Council Directive 2001/83/EC -, the Commission is required to draw up guidance on the collection, verification and presentation of adverse reaction reports. For ease of reading, the guidance included in this chapter is divided into the following areas:

- Adverse reaction reporting
- Reporting requirements in special situations
- Periodic safety update reports
- Company sponsored post-authorisation safety studies

² <http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2a>

- Ongoing risk-benefit evaluation during the post-marketing period

The definitions of relevant terms are provided in the glossary, chapter 3.1.

1.2 Adverse Reaction Reporting

The marketing authorisation holder is responsible for reporting suspected adverse reactions to the authorities of the Member States and the Agency as described in this section.

1.2.1 Scope

For medicinal products authorised through centralised or national procedures, including through mutual recognition, suspected adverse reactions received from health-care professionals should be reported. Spontaneously reported suspected adverse reactions, suspected adverse reactions from post-authorisation studies and those reported in the world-wide literature are included.

A reaction is suspected if either the reporting health-care professional or the marketing authorisation holder believes there is a possible causal relationship between it and the drug in question. Spontaneous reports of suspected adverse drug reactions received from health-care professionals should be reported even if the marketing authorisation holder does not agree with the reporter's assessment of a possible causal association, or if the reporter has not provided a causal assessment. Adverse events which are not suspected of being product-related by the health-care professional attending the patient should not be reported unless the marketing authorisation holder has reason to believe that a causal relationship is possible.

If the marketing authorisation holder is aware that a health-care professional has reported a reaction to one of its products directly to the authority of a member state, the marketing authorisation holder should still report the reaction, informing the authority that the report is likely to be a duplicate of a previous report. In this situation it is essential for the marketing authorisation holder to provide all the available details including any registration number provided to the reporting health-care professional by the authority, in order to aid identification of the duplicate.

Marketing authorisation holders are expected to validate and follow-up all serious reactions reported by them to the authorities. All available clinical information relevant to the evaluation of the reaction should be provided.

1.2.2 Expedited reporting requirements

All expedited reports should be reported immediately and in no case later than 15 calendar days from receipt. The clock for expedited reporting starts as soon as one or more of the following has received the minimum information (an identifiable patient, an identifiable reporter, a suspected reaction, and a suspect drug) required for the submission of an adverse reaction report:

- any personnel of the marketing authorisation holder - including sales representatives,
- the qualified person responsible for pharmacovigilance or persons working for or with this person,
- where the marketing authorisation holder has entered into relationships with a second company for the marketing of, or research on, the suspected product, the clock starts as soon as any personnel of the marketing authorisation holder receives the minimum information; however, wherever possible, the time frame for regulatory submission should be no longer than 15 calendar days from first receipt by the second company and explicit procedures and detailed agreements should exist between the marketing authorisation holder and the second company to facilitate achievement of this objective,

- in the case of relevant world-wide scientific literature, the clock starts with awareness of the publication by any personnel of the marketing authorisation holder; the marketing authorisation holder is expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database, such as Medline, Excerpta Medica or Embase, no less frequently than once a week, or by making formal contractual arrangements with a second party to perform this task; marketing authorisation holders are also expected to ensure that relevant publications in each member state are appropriately reviewed.

1.2.2.1 Spontaneous ADR case reports

i. Serious Adverse Reactions occurring within the EU

The marketing authorisation holder should report, on an expedited basis, all serious suspected adverse reactions, occurring within the European Union and brought to its attention by a health-care professional to the competent authority in the member state in whose territory the incident occurred. For mutually recognised products or products which have been the subject of a referral, these should additionally be reported to the Reference Member State, in accordance with Article 104 of Council Directive 2001/83/EC -

ii. Serious Adverse reactions occurring outside the territory of the EU

- for nationally authorised products, including those authorised through mutual recognition:

The marketing authorisation holder should report, on an expedited basis, all suspected serious unexpected adverse reactions occurring in the territory of a non-EU country and brought to the marketing authorisation holder's attention by a health-care professional in such a way as to be available to the Agency and to all Member States where the medicinal product is authorised. Reports to the Agency should be made electronically using the data processing network foreseen in Article 105 of Directive 2001/83/EC.

- for centrally authorised products:

The marketing authorisation holder should report, on an expedited basis, all suspected serious unexpected adverse reactions occurring in the territory of a non-EU country and brought to the marketing authorisation holder's attention by a health-care professional to the Agency and to all Member States.

However, according to EEA Joint Committee Decision 74/1999³ on the extension of the marketing authorisation procedures of the EU to EFTA states, all serious adverse reactions occurring in the following three EFTA states, Iceland, Liechtenstein and Norway should be submitted by the marketing authorisation holder to the appropriate regulatory authority of the country where the case occurred and do not need to be submitted to the Agency or any Member State, unless they fall into another reporting category. Further according to the above mentioned Decision, all suspected serious unexpected adverse reactions occurring outside the EEA and originally reported by a health care professional should be submitted on an expedited basis also to the appropriate regulatory authority in these EFTA states -

³ OJ L 284 9.11.2000 p.65

iii. Other spontaneous ADR reports

All other ADR reports do not need to be reported on an expedited basis, but should be reported on request or as line listings according to the section on periodic safety update reports, section 1.4. For products which have been authorised through the mutual recognition procedure or which have been the subject of a referral, the marketing authorisation should liaise with the Reference Member State. Any suspected increase in the frequency of serious reactions should also be reported on an expedited basis. The basis on which the frequency assessment has been made should be provided.

Individual adverse reaction reports originating from regulatory authorities within the EEA should be included in the next periodic safety update report, not reported in expedited manner. However, if these regulatory authority reports could lead to a change in the risk-benefit evaluation for the product, this possibility should be communicated to the competent authorities without delay.

1.2.2.2 Case reports from the world-wide literature

Reports from the world-wide literature in accordance with the provisions of section 1.2.1 are considered to be reports of which the marketing authorisation holder can reasonably be expected to be aware and have knowledge.

The marketing authorisation holder is expected to screen the world-wide scientific literature (see section 1.2.2.) and report promptly published suspected serious adverse reactions associated with the use of the active substance(s) of its medicinal products, as relevant to the categories identified in Section 1.2.2.1 i. and ii. above. A copy of the relevant published article should be provided in a language acceptable to the member state.

The MAH is therefore required to report all serious adverse reactions which have occurred within the EEA to the Member or EFTA State in whose territory the incident occurred and all serious unexpected reactions from outside the EEA to all Member States where the product is authorised and to the Agency. As with other reports from outside the EEA, these reports should be provided electronically to the Agency making use of the data-processing network foreseen in Article 105 of Directive 2001/83/EC.

1.2.2.3 Reports from post-authorisation studies

The definition of a post-authorisation study is provided in Section 1.5, Chapter 3, -. Serious suspected adverse reactions occurring in all post-authorisation studies of which the marketing authorisation holder is aware should also be reported on an expedited basis as outlined in the section on spontaneous ADR reporting above. Blinded cases and adverse events not suspected of being due to the study product(s) should not be reported as individual cases. For the management of blinded cases the ICH guideline E2A *Clinical Safety data management: Definitions and standards for expedited reporting* as published in Volume 3C of *The Rules governing medicinal products in the European Union* -- , should be referred to. Thus, cases of serious unexpected reactions should be unblinded by the sponsor prior to reporting. Cases of serious expected reactions should only be reported in expedited manner if the blind has already been broken for some reason. Otherwise, cases of serious expected reactions in blinded studies should be submitted immediately on unblinding at study end. Non-serious adverse events should be included in tabulations in end-of-study reports and do not need to be submitted separately.

For reports from post-authorisation studies which qualify as clinical trials, Directive 2001/20/EC should be applied from the date of its implementation. In the meantime relevant national legislation should be followed in addition to the requirements stated above.⁴

The data elements for individual adverse drug reaction reports are defined in Part IV Chapter 2.1. It is essential for the marketing authorisation holder to provide as many data elements as possible for cases of serious suspected ADRs to facilitate assessment. The information should be as complete as possible.

The minimum information required for the submission of an initial report is an identifiable patient, an identifiable reporter, a suspected reaction, and a suspect drug. In every individual ADR case report, the drug substance/product name shall be provided as reported by the primary reporter.

The original words used by the reporter to describe the adverse reaction should be provided, translated where required into the language of the recipient regulatory authority. The appropriate Lowest Level Terms provided in the latest version of MedDRA (Medical Dictionary for Regulatory Activities) should be used as well.

The marketing authorisation holder is expected to follow-up all reports of serious suspected adverse reactions to its products to obtain comprehensive information where available. Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

Marketing authorisation holders may comment on whether they consider there is a causal association between the suspect product(s) and reactions(s) reported and should provide the criteria on which they have made the assessment.

1.2.3 Reporting forms

Reporting forms acceptable to the competent authorities of the Member States, and to the Agency for centrally authorised products, should be used. However, companies are encouraged to send reports electronically -, using the internationally accepted format (Part IV, chapter 3), MedDRA for the medical terms, and using ICH standards for transmission - -

Computer-generated forms are acceptable provided they are legible and follow an accepted content and layout.

1.2.4 Impact of reported ADRs on the overall safety profile of a product and its Summary of Product Characteristics

In exceptional cases, when a reported ADR impacts significantly on the established safety profile of the product, the marketing authorisation holder should indicate this in the report. Examples might be where the report is one of a series of similar or linked cases which are being simultaneously reported, or where there is prima facie evidence in favour of a causal relationship for a serious and unexpected reaction. Other situations include a suggestion of a change in the nature, severity or frequency of expected ADRs or when new risk factors are identifiable. Information on the frequency of ADRs should also include the basic data on which the estimate of the frequency has been made, including data on the total number of ADR reports and number of patients exposed.

In situations where reported ADRs impact on the established safety profile, the marketing authorisation holder should indicate what action it proposes in relation to the marketing authorisation and the Summary of Product Characteristics.

⁴ It should be noted that, in accordance with Article 18 of Directive 2001/20/EC, the Commission is required to publish detailed guidance on adverse event/reaction reporting.

1.3 Reporting Requirements in Special Situations

Adverse reactions should be considered reportable according to the requirements outlined in the section on expedited reporting regardless of whether or not the medicinal product was used in accordance with the authorised Summary of Product Characteristics (including, for example, prescribed doses higher than those recommended); however, with regard to reporting of overdoses see Section 1.3.6.

There are some situations, which are not covered directly by the reporting requirements detailed in Section 1.2. The recommendations below refer to world-wide experience with the medicinal product.

1.3.1 Reporting in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation

In the period between the submission of the marketing authorisation application, but prior to authorisation, routine single case expedited reporting is not required except according to national law where the product is being used under clinical trial. However, in the pre-authorisation period, information which impacts on the benefit/risk evaluation may become available from the applicant, or Member States where the drug is already in use on a compassionate basis, or from countries where the drug is marketed. It is the responsibility of the qualified person responsible for pharmacovigilance that this information is immediately submitted by the applicant to the competent authority of the Member States where the application is under assessment, and in the case of a centralised application to the Agency, rapporteur and co-rapporteur.

What constitutes a change to the benefit to risk balance is a matter of judgement for the company submitting the dossier but an applicant may be required to justify a decision not to report. For example, normally another report of a well-known adverse reaction would not be considered significant, but a report of an unexpected/new, serious suspected reaction with good evidence of a causal relationship, or reports of a group of cases of such a reaction where there is a possible relationship, or where there is suspicion of a change in the frequency or severity of a known effect would be considered relevant to the evaluation. Similarly results from studies which impact on the assessment of efficacy would be significant.

1.3.2 Reporting of outcomes of use during pregnancy

Marketing authorisation holders are expected to follow up all reports from health-care professionals of pregnancies where the foetus could have been exposed to one of its medicinal products. Where reports originate from consumers, reasonable attempts should be made at follow-up via the patient's health-care professional. When an active substance, or one of its metabolites, has a long half life, this should be taken into account when considering whether a foetus could have been exposed (i.e. medicinal products taken before the gestational period need to be considered).

If a pregnancy results in an abnormal outcome which the reporting health-care professional considers might be due to the drug, this should be treated as an expedited report and should follow the reporting requirements outlined in Sections 1.2.2.1.i. and ii..

These cases together with other reports of abnormalities in pregnancy should also be included in the PSUR together with aggregated data of overall exposure and details of normal/abnormal outcomes. Reports from prospective registries should also be included and evaluated in the PSUR.

If, in the period between PSURs, a marketing authorisation holder becomes aware of a signal of a possible teratogenic effect (e.g. a cluster of similar abnormal outcomes) all regulatory authorities where a marketing authorisation is held, and also the Agency in the case of centrally authorised medicinal products, should be informed immediately.

1.3.3 Reporting from other post-marketing initiatives: surveys, registries

A marketing authorisation holder may be involved in post-marketing initiatives, which result in the collection of information related to its products. In these situations, there is a distinction to be made between where there is a systematic process for reporting of adverse events to the marketing authorisation holder and where no such process exists. Only those events which are specifically reported as suspected serious adverse reactions to a particular drug are subject to expedited reporting. Reporting requirements should be dealt with in the same way as expedited reports from post-authorisation studies and the requirements outlined in Section 1.2 should be followed.

1.3.4 Compassionate use/named patient supplies

Compassionate or named patient use of a drug should be strictly controlled by the company responsible for providing the drug and should ideally be the subject of a protocol. The protocol should ensure that the patient is registered and adequately informed about the nature of the medicine and that both the prescriber and the patient are provided with the available information on the properties of the medicine with the aim of maximising the likelihood of safe use. The protocol should encourage the prescriber to report any adverse reactions suspected of being related to use of the medicine to the company and to the competent authority where required on a national basis. Companies should continuously monitor the balance of benefit and risk of drugs used under such conditions and follow the requirements for reporting to the appropriate competent authorities.

1.3.5 Lack of efficacy

Reports of lack of efficacy should not normally be expedited, but should be discussed in the relevant periodic safety update report. However in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. Medicinal products used for the treatment of life-threatening diseases, vaccines and contraceptives are examples of classes of medicinal products where lack of efficacy should be considered as expedited reports. Judgement should be used in reporting. For example, antibiotics used in life-threatening situations where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, life-threatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible should be reported on an expedited basis.

Lack of efficacy for anti-neoplastic agents should not be routinely reported as an expedited report unless the lack of efficacy indicates a change in the benefit to risk balance - for example a lower than expected efficacy or a higher than expected number, or rate, of deaths due to progressive disease.

1.3.6 Reporting of overdoses and abuse

The marketing authorisation holder should report cases of overdose and abuse that lead to suspected serious (EU) or serious and unexpected (outside EU) adverse reactions on an expedited basis to the appropriate competent authority in accordance with the requirements in Section 1.2.

This should include reports that indicate that the taking of the suspect drug led to suicidal intention and a subsequent overdose of the suspect drug or other medication.

Reports of overdose and abuse with no associated adverse reactions should not be reported as adverse reactions. They should be routinely followed up to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome.

1.3.7 Reporting of misuse

The marketing authorisation holder should collect any available information related to its products on misuse, which may have an impact on the evaluation of their benefits and risks and report cases of

misuse that lead to suspected serious (EU) or serious unexpected (outside EU) adverse reactions on an expedited basis to the appropriate competent authority.

1.4 Periodic Safety Update Reports

1.4.1 Introduction

Once a medicinal product is authorised in the EU, even if it is not marketed, the marketing authorisation holder is required to submit a PSUR. PSURs are normally required to be prepared at 6-monthly intervals for the first two years following the medicinal product's authorisation in the EU, annually for 2 years, at the first renewal, and then 5-yearly at renewal thereafter. There may, however, be exceptions where the cycle may be re-started or an exemption to the requirement for 6-monthly and annual PSURs is granted. This is explained in Section 1.4.2.5.2..

For medicinal products authorised under the centralised procedure PSURs should be submitted to the competent authorities of all countries of the EEA and to the Agency in accordance with Council Regulation (EEC) No 2309/93 Articles 21 and 22, Commission Regulation (EC) 540/95 Articles 2 and 3 and the relevant EEA Agreements and related Decisions of the EEA Joint Committee (see list on Distribution Requirements for PSURs in Annex 1). At these times marketing authorisation holders are expected to provide succinct summary information together with a critical evaluation of the benefit to risk balance of the product in the light of new or changing post-authorisation information. This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorisation, the Summary of Product Characteristics (SPC), patient information leaflet or product advertising.

1.4.2 General principles

1.4.2.1 One report for products containing one active substance authorised to one marketing authorisation holder

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance for medicinal products authorised to one MAH may be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications or populations (e.g. children vs. adults) may be appropriate.

If a subsequent marketing authorisation is granted to a marketing authorisation holder for a product which contains the same active substance as one previously granted to the same marketing authorisation holder, the data lock points used for the PSURs for the first product should normally be used for the following joint PSURs covering the first and all subsequent products. However the submission cycle will normally restart with the granting of a subsequent marketing authorisation unless other conditions are laid down within the terms of the granting of the marketing authorisation (see Section 1.4.2.5.2). In such a case, the joint PSURs submitted according to the cycle for the latest marketing authorisation cover data for all previous products.

1.4.2.2 Combination products

For combinations of substances which are also authorised individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered essential.

1.4.2.3 General scope of information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorisation applications and renewals,

and data on serious, unlisted ADRs (see Section 1.4.2.6.). These should be provided for both the period in question and as cumulative summary tabulations starting from the International Birth Date.

The main focus of the report should be adverse drug reactions (ADRs). Unless indicated otherwise by the reporting health-care professional, all adverse experiences reported spontaneously should be assumed to be adverse drug reactions; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions and for certain other medicinal products, e.g. contraceptives and vaccines (see Section 1.3.5.), may represent a significant hazard, and in that sense be a safety issue. These types of cases should be discussed within the PSUR (see Section 1.4.3.8.1.).

An increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although such increased reporting should be discussed in the PSUR, it is not possible to provide specific guidelines as to what constitutes increased reporting or what method should be used for quantifying this. Marketing authorisation holders should provide details of the methods that have been used. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change (e.g. population exposed, duration of exposure).

1.4.2.4 Products authorised to more than one marketing authorisation holder

Where a product is authorised to more than one marketing authorisation holder, the submission of joint Periodic Safety Update Reports (PSURs) is acceptable provided that the products remain identical as defined in Section 1.1.1.1 and provided that the PSURs are submitted independently by or on behalf of the respective marketing authorisation holder for its product. The data lock point should be based on the birth date used for the first authorised product.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting marketing authorisation holder's product information, these data should be included, with source indicated, and discussed in the PSUR, even if it is known that they are included in another marketing authorisation holder's PSUR.

1.4.2.5 Frequency of review and reporting

1.4.2.5.1 PSUR reporting requirements

PSURs should be submitted at the following times from the EU Birth Date, for all medicinal products unless the marketing authorisation makes different provisions (see Sections 1.4.2.5.2 and 1.4.2.5.3):

- immediately upon request
- 6-monthly for the first 2 years after authorisation
- annually for the subsequent 2 years
- at the first renewal
- thereafter 5-yearly at renewal.

Multiples of 6-monthly PSURs, are acceptable, provided that the marketing authorisation holder submits a PSUR bridging summary report the content of which is described in Section 1.4.4.

Data lock points may be set according to the EU Birth Date of a medicinal product or its International Birth Date. Definitions for data lock point, EU Birth Date and International Birth Date (IBD) are given in the glossary, Part I, chapter 3.1.

Each PSUR should cover the period of time since the last update report and should be submitted within 60 days after the last data lock point.

The marketing authorisation holder should submit the PSUR together with the renewal application at least three months before the expiry date of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate co-ordination with the regular cycle of the PSUR. Marketing authorisation holders should lock their data no more than 60 days before submitting the application for renewal. The PSUR should cover the intervening time period since the last PSUR. (With regard to mutually recognised products also *Notice to Applicants, Volume 2C of the Rules Governing Medicinal Products in the European Union*, Guideline on the processing of renewals in the mutual recognition procedure). For the first renewal, the last 6 monthly PSUR should be provided; for the subsequent renewal, it can be provided either a single 5 years PSUR or separate 6 monthly or yearly PSURs covering 5 years together with a PSUR bridging summary report described in section 1.4.4.

1.4.2.5.2 Circumstances where the PSUR submission cycle may be amended

The submission of PSURs is part of the normal conditions of marketing authorisation. More frequent submissions may be required as a condition of authorisation. In certain circumstances less frequent submissions may be appropriate.

Where an amendment is proposed, the applicant should submit, as part of the application for a marketing authorisation, a reasoned request for the amendment which, if granted, becomes part of the conditions of authorisation. If an amendment is applied for after authorisation, such an application should follow the procedures for a type II variation.

If the request for an amendment is granted, the competent authority will specify the amendments. Submission of PSURs at a lower frequency than once every five years is not possible as the PSUR is an integral part of the authorisation renewal application. There may be circumstances where the authorities require an amendment of the cycle.

Areas where an amendment to the cycle of PSURs may be considered include:

- New indications, dosage forms, routes of administration or populations beyond the initial authorisation for the active substance
- New authorisation for a medicinal product with:
 - the same qualitative and quantitative composition in terms of active principles and excipients and
 - the same pharmaceutical form and the same route of administration as a previously authorised medicinal product

The previously authorised medicinal product should have been widely used in one or more Member States for the same indication(s) and should have a well-recognised efficacy and an acceptable level of safety in the same indications(s).

- Where a medicinal product authorised in the EU through mutual recognition had an authorisation in the reference member state for a year or more prior to mutual recognition

If there has been a long period between the launch of a product anywhere in the world and the date of the authorisation (i.e. more than one year), the PSUR periodicity may be revised. An anniversary of the birth date occurring during the year preceding first launch may be chosen for purposes of determining the subsequent periodicity of the PSURs.

1.4.2.5.3 Preparation of PSURs according to the International Birth Date

Medicinal products, which are also authorised outside the EU, will have an International Birth Date (IBD). This is the date of the first marketing authorisation for the product granted to the marketing authorisation holder in any country in the world. For medicinal products first authorised in the EU, the EU Birth Date is the IBD. For administrative convenience, if desired by the marketing authorisation holder, the IBD may be designated as the last day of the same month.

In order to harmonise periodic safety updates internationally, the marketing authorisation holder, may use the IBD to determine the data-lock points in the EU rather than the EU Birth Date. If the IBD is used, the first data lock point must be within 6 months of the EU Marketing Authorisation Date, unless other requirements have been laid down at the time of granting the authorisation. Regardless of whether the IBD or EU Birth Date is used, the PSUR must always be submitted within the 60 days following the data lock point.

1.4.2.6 Reference safety information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accordance with previous knowledge on the medicinal product's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison.

Having one reference source of information would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for marketing authorisation holders to prepare their own "Company Core Data Sheet" (CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each marketing authorisation holder to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as "Company Core Safety Information" (CCSI).

For the purposes of periodic safety reporting, the CCSI forms the basis for determining whether an adverse drug reaction is already listed or is still unlisted, terms which are introduced to distinguish them from the usual terminology of expectedness which is used in association with the approved product information. The EU SPC or locally approved product information continues to be the reference document upon which expectedness is based for the purpose of local expedited post-authorisation safety reporting.

1.4.2.7 Presentation of data on individual case histories

1.4.2.7.1 Sources of information

Generally, data from the four following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

- i. Direct reports to marketing authorisation holder (or under MAH control):
 - spontaneous notifications from health-care professionals

- marketing authorisation holder sponsored clinical studies or named patient (compassionate) use
- ii. Literature
- iii. ADR reporting systems of regulatory authorities :
 - spontaneous notifications and non-spontaneous notifications
- iv. Other sources of data:
 - reports on ADRs exchanged between contractual partners (e.g. licensors-licensees)
 - data in special registries, such as maintained in organ toxicity monitoring centres
 - reports created by poison control centres
 - epidemiological databases

1.4.2.7.2 Description of the reaction

The reaction terms used in the PSUR will generally be derived from whatever standard terminology (“controlled vocabulary” or “coding dictionary”) is used by the reporting marketing authorisation holder.

Whenever possible, the notifying reporter’s reaction terms should be used to describe the ADR. However, when the notifying reporter’s terms are not medically appropriate or meaningful, marketing authorisation holders should use the best alternative compatible reaction terms from their ADR dictionaries to ensure the most accurate representation possible of the original terms. Under such circumstances, the following should be borne in mind:

- in order to make it available on request, the “verbatim” information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable)
- in the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the marketing authorisation holder and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data
- if a marketing authorisation holder disagrees with a diagnosis that is provided by the notifying health-care professional, it may indicate such disagreement within the line listing of cases (see Section 1.4.3.7.3).
- marketing authorisation holders should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the marketing authorisation holder’s medical interpretation (identified by asterisk or other means).

1.4.2.7.3 Line listings and/or summary tabulations

Depending on their type or source, available ADR cases should be presented as line listings and/or as summary tabulations (see Tables 2.2 and 2.3, Annex 2).

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting full case reports.

Marketing authorisation holders should prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see Section 1.4.2.7.1.i.) as well as those received from regulatory authorities. They should usually do the same for published cases (usually well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see Section 1.4.2.7.1.iv.) might not be (1) possible without standardisation of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the marketing authorisation holder. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g. all serious ADRs and all non-serious unlisted ADRs), but also on other cases for which line listings are not requested (e.g. non-serious listed ADRs). Details are found in Section 1.4.3.6.3. and 1.4.3.6.4.

1.4.3 Model for a Periodic Safety Update Report (PSUR)

The following sections are organised as a sample PSUR. In each of the sections, guidance is provided on what should be included.

1.4.3.1 Introduction

The marketing authorisation holder should briefly introduce the product so that the report “stands alone” but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g. for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another marketing authorisation holder, some of whose data are included in the report (see Section 1.4.2.4.), the possibility of data duplication should be noted.

1.4.3.2 World-wide marketing authorisation status

This section of the report provides cumulative information.

The following information should be provided, usually as a table, for all countries where a regulatory decision about marketing has been made related to the following:

- dates of market authorisation, and subsequent renewal;
- any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;

- treatment indications and special populations covered by the market authorisation, when relevant;
- lack of approval, including explanation, by regulatory authorities;
- withdrawal by the company of an authorisation application submission if related to safety or efficacy;
- dates of launch;
- trade name(s).

Typically, indications for use, populations treated (e.g. children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorised. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures.

If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorisations.

Table I of part IV, chapter 2 provides an example, with fictitious data for an antibiotic, of how such a table might be organised. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

1.4.3.3 Update of regulatory authority or marketing authorisation holder actions taken for safety reasons

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission:

- marketing authorisation withdrawal or suspension;
- failure to obtain a marketing authorisation renewal;
- restrictions on distribution;
- clinical trial suspension;
- dosage modification;
- changes in target population or indications;
- formulation changes
- urgent safety restrictions.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health-care professionals (e.g. Dear Doctor letters) as a result of such action should also be described with copies appended.

1.4.3.4 Changes to reference safety information

The version of the “Company Core Data Sheet” (CCDS) with its “Company Core Safety Information” (CCSI) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PSUR and include the date of the last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists and consumers. Therefore, during that period the amended reference document (CCDS) may contain more “listed” information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the EU SPC (or the official data sheets/product information documents approved in a country), a brief comment should be prepared by the marketing authorisation holder, describing the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

1.4.3.5 Patient exposure

Where possible, an estimate of patient exposure should cover the same period as the interim safety data. While it is recognised that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially paediatric vs. adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other breakdown (e.g. indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

1.4.3.6 Presentation of individual case histories

1.4.3.6.1 General considerations

Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.

With regard to the literature, marketing authorisation holders should monitor standard, recognised medical and scientific journals for safety information relevant to their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources.

Care should be taken to include such cases only once. Also, no matter what “primary source” is given a case, if there is a publication, it should be noted and the literature citation given.

In the EU, no countries require submission of medically unconfirmed spontaneous reports that originate from consumers or other non-health care professionals, although such reports are accepted or requested in other countries. Medically unconfirmed reports should, therefore, be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

1.4.3.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (see Table 2.3, Annex 2). Attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources.

- all serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
- all serious reactions (attributable to the medicinal product by either investigator or sponsor), available from studies or named-patient (compassionate) use;
- all serious reactions, and non-serious unlisted reactions, from the literature;
- all serious reactions from regulatory authorities.

Collection and reporting of non-serious, listed ADRs may not be required in all EU countries. Therefore, a line listing of spontaneously reported non-serious listed reactions that have been collected should be submitted as an addendum to the PSUR only when requested by a regulatory authority.

1.4.3.6.3 Presentation of the line listing

The line listing(s) (see Table 2.3, Annex 2) should include each patient only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis), as judged by the marketing authorisation holder.

It is possible that the same patient may experience different ADRs on different occasions (e.g. weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same patient might then be included in a line listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organised (tabulated) by body system (standard organ system classification scheme).

Where joint PSURs for co-marketed products are submitted, the line listings should still reflect the name of the active substance/medicinal product as reported by the primary reporter.

The following headings should usually be included in the line listing (see Table 2.3, Annex 2):

- Marketing authorisation holder case reference number
- Country in which case occurred
- Source (e.g. clinical trial, literature, spontaneous, regulatory authority)
- Age and sex
- Daily dose of suspected medicinal product (and, when relevant, dosage form or route)

- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in comments section).
- Dates of treatment. If not available, best estimate of treatment duration.
- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary) (see Section 1.4.2.7.2 for guidance).
- Patient outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown). This should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect medicinal product(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

1.4.3.6.4 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations usually contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g. by source of report). See Table 2.2, Annex 2, for a sample data presentation on serious reactions.

A summary tabulation should be provided when necessary for the non-serious, listed, spontaneously reported reactions (see also Section 1.4.3.6.2).

The terms used in these tables should ordinarily be those used by the marketing authorisation holder to describe the case (see Section 1.4.2.7.2).

Except for cases obtained from regulatory authorities, the data on serious reactions from other sources (see Section 1.4.2.7.1.iv.) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e. all cases reported to date) should be provided in the table(s) or as a narrative.

1.4.3.6.5 Marketing authorisation holder's analysis of individual case histories

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.)⁵ The focus here should be on individual case

discussion and should not be confused with the global assessment in the overall safety evaluation (see Section 1.4.3.9).

1.4.3.7 Studies

All completed studies (non-clinical, clinical, and epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

1.4.3.7.1 Newly analysed studies

All relevant studies containing important safety information and newly analysed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

1.4.3.7.2 Targeted new safety studies

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g. objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analysed, the final results should be presented in a subsequent PSUR as described under Section 1.4.3.7.1.

1.4.3.7.3 Published studies

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarised and publication reference(s) given.

1.4.3.8. Other information

1.4.3.8.1. Efficacy-related information

For a product used in prevention or to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

1.4.3.8.2 Late-breaking information

Any important, new information received after the database was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the overall safety evaluation (see Section 1.4.3.9).

1.4.3.9 Overall safety evaluation

The marketing authorisation holder should provide a concise analysis of the data presented, taking into account any late-breaking information (see Section 1.4.3.8.2), and followed by the marketing authorisation holder's assessment of the significance of the data collected during the period. The marketing authorisation holder should also review the cumulative experience and highlight any new information on:

- a change in characteristics of listed reactions, e.g. severity, outcome, target population
- serious unlisted reactions, placing into perspective the cumulative reports
- non-serious unlisted reactions
- an increased reporting frequency of listed reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):

- drug interactions
- experience with overdose, deliberate or accidental, and its treatment
- drug abuse or misuse
- positive or negative experiences during pregnancy or lactation
- experience in special patient groups (e.g. children, elderly, organ impaired)
- effects of long-term treatment.

1.4.3.10 Conclusion

The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);
- specify and justify any action recommended or initiated.

Having made the decision to amend the SPC, the marketing authorisation holder should submit the variation application at the same time as the PSUR, or where this is not possible, should state a timetable for submission.

1.4.4 Contents of the PSUR bridging summary report

The summary report should not repeat the information already included in the PSUR. If there is a need the applicant should cross refer to relevant sections of the appropriate PSURs. The bridging summary report should include the following contents:

1. Exposure estimation for the period covered expressed in number of patients ~~should be included~~;
2. Cumulative summary tabulations ordered by organ class, seriousness and listedness;
3. An overview of safety concerns which emerged, resolved or still outstanding during the whole period.

1.5 Company-Sponsored Post-Authorisation Safety Studies

It is well recognised that there is a continuous need to monitor the safety of medicines as they are used in clinical practice. Spontaneous reporting schemes provide important early warning signals of potential product hazards and also provide a means of continuous surveillance. Formal studies to

evaluate safety may also be necessary, particularly in the confirmation, characterisation and quantification of possible hazards identified at an earlier stage of product development or during marketed usage (see Section 1.6.1.1). Such studies may also be useful in identifying previously unsuspected reactions or in confirming the safety profile of a medicine under marketed conditions.

The guidance on *Good Clinical Practice*⁶ does not apply to observational pharmacoepidemiological studies.

1.5.1 Scope of the guidance in this section

This section applies to the conduct of studies sponsored or partly sponsored by the pharmaceutical industry which evaluate the safety of products with a marketing authorisation in humans:

They encompass all company-sponsored studies, which are carried out to evaluate the safety of authorised medicines. This includes studies where the medicine is provided by the sponsoring company and those where it is prescribed in the normal way, both in general practice and in the hospital setting.

They provide a framework whereby a variety of data collection methods can be used to evaluate the safety of authorised medicines. Whilst it is recognised that the study design used needs to be tailored to particular products and hazards, the guidance in this section defines the essential principles to be applied in a variety of situations. The study methods in this field continue to develop and therefore there will be a need to regularly review the guidance in this section to ensure that it reflects advances made in the assessment of product safety. In addition, this section will need to be reviewed once *Directive 2001/20/EC* on implementation of Good Clinical Practice -has been implemented by all Member States.

The definition of a post-authorisation safety study is provided in the glossary, Part I, chapter 3.

This section relates principally to those studies where there is a known safety issue under investigation and/or when the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s). A hazard may be unexpectedly identified in the course of performing a study on an authorised product which would normally fall outside the scope of these guidelines. In that case, the marketing authorisation holder and specifically the named person responsible in pharmacovigilance is expected to inform the relevant regulatory authorities immediately and to provide a brief report on progress at intervals and at study end as requested by the authorities.

After a product has been placed on the market, clinical trials exploring e.g. new indications, new methods of administration or new combinations, are considered to be trials for new medicinal products and are not covered by the guidance in this section.

In cases of doubt as to whether or not a study comes under the jurisdiction of the guidance in this section the company should discuss the intended protocol with the relevant regulatory authorities of the member state(s) in which the study is to be conducted.

1.5.2 Extent and objectives of post-authorisation safety studies

Post-authorisation studies may be conducted for the purpose of identifying previously unrecognised safety issues (hypothesis-generation), investigating possible hazards (hypothesis-testing in order to substantiate a causal association) or confirming the expected safety profile of a medicinal product under marketed conditions. They may also be conducted to quantify established adverse reactions and to identify risk factors.

⁶ Volume 3C of The Rules Governing Medicinal Products in the European Union, Eudralex

Situations where studies may be appropriate include:

- for a medicine with a novel chemical structure or novel mode of action
- where there is uncertainty as to the clinical relevance of a toxic effect in animals
- where there is uncertainty as to the safety profile
- where there is a need to better quantify adverse effects identified in clinical trials and elucidate risk factors
- where there is a highly specific use requiring specialist monitoring.

A variety of designs may be appropriate including observational cohort studies, case-surveillance or case-control studies. Clinical trials involving systematic allocation of treatment (for example, randomisation) may also be used to evaluate the safety of authorised products. Such clinical trials should also comply with the guidelines on *Good Clinical Practice* (see Section 1.5.3.4).

The design to be used will depend on the objectives of the study, which must be clearly defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods.

1.5.3 Design of studies

1.5.3.1 Observational cohort studies

Patients must not be prescribed particular medicines in any way other than would have occurred in normal medicinal practice. In order for a study to be considered observational, there must be no constraints on the prescribing physician or influences on normal clinical practice.

The population studied should normally be as representative as possible of the general population of users, and be unselected unless specifically targeted by the objectives of the study (for example a study of the elderly). Exclusion criteria should be limited to the contraindications stated in the SPC. In prospective studies the doctors involved in the study should be provided with the SPC for all products to be used. Where the product is used outside the indications of the SPC at the discretion of the prescribing doctor, such patients should be included in the analysis of the study findings.

Observational cohort studies should normally include appropriate comparator group(s). The comparator group(s) will usually include patients with the disease/indication(s) relevant to the primary study product and such patients will usually be treated with alternative therapies.

The medicinal product(s) should be prescribed in the usual manner, for example on a form written by the responsible physician or through the usual hospital procedures.

The decision to prescribe a product must be clearly separated from the decision to include that patient in the study. The justification for using the medicine must be recorded by the prescribing doctor in the patient's records within the study documents.

The protocol should stipulate the minimum and maximum number of patients to be entered by a single doctor.

1.5.3.2 Case-control studies

Case-control studies are usually conducted retrospectively. Comparison is made between the product exposure of “cases” with the disease/event of interest and appropriate controls without the disease/event. The study design should attempt to account for known sources of bias and confounding.

1.5.3.3 Case-surveillance

The purpose of case-surveillance is to study patients with diseases for which some cases are likely to be product-related and to ascertain product exposure. Marketing authorisation holders who sponsor such studies should liaise particularly closely with the relevant regulatory authorities in order to determine the most appropriate arrangements for the reporting of cases.

1.5.3.4 Clinical trials

Specific clinical trials are sometimes necessary to clarify the mechanisms of adverse reactions and to identify the means of prevention (e.g. pharmacokinetic, pharmacodynamic or pharmaco-genetic studies). Large clinical trials may also be useful in the investigation of post-authorisation safety issues and these may involve random allocation to treatment. In other respects, an attempt should be made to study patients under as normal conditions as possible. Exclusion criteria should normally be limited to the contraindications in the Summary of Product Characteristics (SPC) unless they are closely related to the particular objectives of the study. Clinical trials should also adhere to the guidelines on *Good Clinical Practice*. Post-authorisation studies which qualify as clinical trials should also adhere to the Directive 2001/20/EC, once implemented, and until then with relevant national legislation and *Good Clinical Practice* guidelines.

1.5.4 Conduct of studies

Responsibility for the conduct of the study shall be vested in the sponsor, usually the marketing authorisation holder’s medical department. It shall be supervised by designated monitor(s) sited in the member state(s) in which the study is to be conducted, and whose names shall be recorded in the study documents.

Consideration should be given to the appointment of an independent advisory group(s) to monitor the data and oversee the study.

1.5.5 Liaison with regulatory authorities

Marketing authorisation holders proposing to perform a post-authorisation study are advised to discuss the draft protocol at an early stage with the relevant regulatory authorities and independent experts. Particular consideration should be given to specific safety issues, which may require investigation. National legislative requirements or guidelines should be taken into account in those Member States where these exist.

Before the study commences a protocol must be finalised which explains the aims and objectives of the study, the methods to be used (including statistical analysis and justification of sample size) and the record keeping which is to be maintained. The marketing authorisation holder should submit the protocol plus any proposed communications to doctors to the relevant regulatory authorities at least one month before the planned start of the study. The authorities may comment as necessary. The responsibility for the conduct of the study will, however, rest with the sponsoring pharmaceutical company.

The marketing authorisation holder should inform the relevant regulatory authorities when the study has commenced and will normally provide a brief report on its progress every six months, or as requested by the authorities.

For cohort studies, the following content of progress reports is recommended:

- Tabulation of numbers of patients identified as suitable for the study, patients entered and patients followed-up
- Estimate of overall exposure to study product(s) in patient-years or months or days
- Status of all patients who have completed the study, e.g. on/off treatment, deceased, lost to follow-up
- Tabulation of the reasons for stopping treatment during the study
- Individual listing of causes for each death and case hospitalised
- Table of all serious adverse events (numerical form plus a line listing).

N.B. If there are multiple study products, data should be reported for each product separately.

Generally only the data listed above should be included. Other information should not be included without prior discussion with the appropriate regulatory authorities. After review of the report, regulatory authorities may request additional information.

The usual regulatory requirements for reporting of suspected adverse reactions must be fulfilled. marketing authorisation holders should ensure that they are notified of serious suspected adverse reactions and should report these to the relevant regulatory authorities immediately and no later than 15 calendar days of receipt. Non-serious adverse reactions and events, which are not suspected by the investigator to be adverse reactions, should not be reported individually, but they should be summarised in the final report. Reports of serious adverse reactions occurring in post-authorisation studies should also be included in the periodic safety update report. The qualified person responsible for pharmacovigilance should provide to the competent authorities any other information relevant to the evaluation of the benefits and risks afforded by the medicinal product, including appropriate information on post authorisation safety studies.

A final report on the study should be sent to the relevant regulatory authorities within 3 months of follow-up being completed. Ideally this should be a full report but a brief preliminary report within 3 months followed by a full report within 6 months of completion of the study would normally be acceptable. Marketing authorisation holders should follow the *Good Clinical Practice* guidelines on the content of final reports. The findings of the study should be submitted for publication.

In the case of products authorised through the centralised procedure, progress reports and final reports should also be sent to the Agency.

These may require adaptation to suit the needs of individual studies.

1.5.6 Promotion of medicines

Post-authorisation studies should not be planned or conducted for the purposes of promoting the use of medicines.

Company representatives should not be involved in studies in such a way that it could be seen as a promotional exercise.

1.5.7 Doctor participation

Subject to the doctor's terms of service, payment may be offered to the doctor in recompense for any additional time and expenses incurred according to a scale of fees agreed nationally.

No inducement for a doctor to participate in a post-authorisation study should be offered, requested or given.

1.5.8 Ethical issues

The highest possible standards of professional conduct and confidentiality must always be maintained and any relevant national legislation on data protection followed. The patient's right to confidentiality is paramount. The patient's identity in the study documents should be codified, and only authorised persons should have access to identifiable personal details if data verification procedures demand inspection of such details. Identifiable personal details must always be kept in confidence. (See also *Good Clinical Practice* guidelines.)

Responsibility for the retrieval of information from personal medical records lies with the medical practitioner(s) responsible for the patient's care. Such information should be directed to the medical practitioner nominated by the sponsor, who is thereafter responsible for the handling of such information.

Reference to an Ethics Committee is required if patients are to be approached for information, additional investigations are to be performed, or if it is proposed to allocate patients systematically to treatments.

1.5.9 Procedure for complaints

A post-authorisation study, which gives cause for concern, should be referred to the relevant regulatory authorities, or, if appropriate, to other bodies within Member States which are deemed to have the matter within their remit.

1.6 On-Going Pharmacovigilance Evaluation During the Post-Authorisation Period

The granting of a marketing authorisation for a medicinal product indicates that it is considered to have a satisfactory balance of benefits and risks under the conditions defined in the SPC, on the basis of the information available at that time.

During the post-authorisation period the product will be used in a setting different from clinical trials and larger populations are likely to be exposed. Much new information will be generated which may impact on the benefit or risk of the product, and evaluation of this information needs to be an on-going process, both within pharmaceutical companies and regulatory authorities.

Both, marketing authorisation holders and regulatory authorities must keep abreast of all relevant information in order to fulfil the following responsibilities:

- ensuring that appropriate action is taken in response to new evidence which impacts on the balance of benefits to risks,
- keeping health care professionals and patients informed through changes to authorised product information and by direct communication.

The legal responsibilities of the marketing authorisation holder, and in particular the qualified person responsible for pharmacovigilance, are provided in Section 1.1.1. of this chapter. It is the responsibility of the qualified person responsible for pharmacovigilance to provide to the competent

authority any information relevant to the evaluation of benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation safety studies.

In the event of any new or changing information becoming available which may influence the overall benefit-risk assessment of a medicinal product, the marketing authorisation holder should immediately inform all the competent authorities in the countries in which the product is authorised, and in addition, for products which are authorised centrally, the Agency secretariat. Where the competent authority identifies new or changing information which may influence the overall benefit-risk assessment it is usually appropriate that they communicate this concern to the marketing authorisation holder at the time that such information is shared with other competent authorities. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted at the earliest opportunity and no later than the agreed date specified in the written communications between the competent authority and the marketing authorisation holder. It should be sent to all competent authorities of the Member States in which the medicinal product has been authorised, and in addition, for products, which are authorised centrally, the Agency secretariat.

The competent authorities are responsible for providing reports of serious adverse reactions occurring in their member state to the relevant marketing authorisation holder within 15 calendar days of receipt.

The following sections

- provide the principles on which an assessment of the balance of benefits and risks should be based and
- outline the steps that marketing authorisation holders and competent authorities can take in order to address a change in the balance of benefit and risks.

1.6.1 Principles of benefit-risk assessment

Overall benefit-risk assessment should take into account and balance all the benefits and risks referred to below. Benefit-risk assessment should be conducted separately in the context of each indication, which may impact on the conclusions and actions.

1.6.1.1 Assessment of benefits

When a new or changing hazard is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use. Benefit is composed of three parameters: (1) the extent to which the medicinal product cures or improves the disease, or relieves the symptoms, (2) the responder rate, (3) the duration of response. Any available information on misuse of the product and on the level of compliance in clinical practice, which may have an impact on the evaluation of its benefits, should also be considered. The quality of the different types of evidence of benefit should be taken into account. Efficacy and benefit should, as far as possible, be expressed in quantitative terms in a way that makes them comparable to the expression of risks.

1.6.1.2 Assessment of risks

- Assessment of risk involves a stepwise process requiring identification, confirmation, characterisation (including identification of the determinants of risk), and quantification of product safety hazards in the exposed population. Overall assessment of risk should consider all sources of information, including : national and international spontaneous ADR reports
- ADR-data from observational and experimental clinical studies which may or may not be company-sponsored

- in vitro and in vivo laboratory experiments
- world-wide scientific literature
- registries of congenital anomaly/birth defects
- investigations on pharmaceutical quality
- data on sales and product usage.

When possible product safety hazards are identified which have an impact on, or may influence the overall benefit to risk of a medicinal product, the marketing authorisation holder should propose appropriate studies. Such studies should investigate further the nature of the hazard(s) and their frequency of occurrence, provided that such studies would not cause unacceptable risk to the patients involved. Such studies should comply with the guidance provided in section 1.5 of these chapter.

Important issues, which should be addressed in the assessment of risk, include: evidence for causal association, seriousness, absolute and relative frequency, and presence of risk determinants, which may allow preventative measures.

The quality of the different types of evidence of risk should be taken into account.

1.6.1.3 Benefit-risk assessment

Whenever possible, both benefits and risks should be considered in absolute terms and in comparison to alternative treatments. The degree of risk that may be considered acceptable is dependent on the seriousness of disease being treated. For example:

- In the treatment of a disease with high mortality, a high risk of serious adverse reactions may be acceptable providing the benefits associated with treatment have been shown to be greater.
- For medicines used in chronic diseases or in prevention of disabling diseases, some level of risk may be acceptable if there is a substantial improvement in the prognosis or quality of life.
- In situations where the main benefit is symptom relief for minor illnesses in otherwise healthy individuals or where individuals are treated not only for their own benefit but also for the benefit of the community (e.g. vaccination) safety standards must be exceptionally high.

1.6.2 Improving the benefit to risk balance

The marketing authorisation holder should aim to achieve as high as possible benefit to risk balance for an individual product and ensure that the adverse consequences of a medicinal product do not exceed the benefits within the population treated. The benefit-risk profile of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The benefit to risk can be improved either by increasing the benefits, or by reducing the risks by minimising risk factors (e.g. by contra-indicating the use in patients particularly at risk, or lowering dosage, introducing pre-treatment tests to identify patients at risk, or monitoring during treatment for early diagnosis of hazards that are reversible). When proposing measures to improve the benefit to risk of a product (e.g. by restricting use to a patient group most likely to benefit or to where there is no alternative) their feasibility in normal conditions of use should be taken into account.

The following types of action may be necessary and can be undertaken voluntarily by marketing authorisation holders or compulsorily by competent authorities in accordance with legislation:

- Variation of the marketing authorisation in respect of the indications, dosage recommendations, contraindications, warnings or adverse effects and in consequence:
 - modification of the SPC and the patient information leaflet in line with the marketing authorisation;
 - modification of advertising material.
- Direct provision of important safety information to health-care professionals (e.g. through letters and/or bulletins).

If there are important new safety concerns, marketing authorisation holders should submit urgent safety restrictions in accordance with Commission Regulations EC No 1084/2003 and 1085/2003(ex. 541/95 and 542/95 Commission Regulations) - These measures must be immediately communicated to the relevant regulatory authorities. If no objections are raised within 24 hours of a valid application, the urgent safety restrictions may be introduced and the corresponding application for the variation submitted immediately to the competent authorities and with respect to centrally authorised medicinal products, the Agency. An urgent safety restriction can also be initiated by the competent authorities and the Commission. . From 1 October 2003 the corresponding application shall be submitted no later than 15 days after the initiation of the urgent safety restriction-

When any significant alteration to the safety information in an SPC is made, the appropriate health-care professionals must be informed promptly and provided with the new SPC. The patient information leaflet should also be updated and made available with the product (see Section 1.6.4.).

1.6.3 Withdrawal of a product from the market on risk-benefit grounds

In the event that the overall benefit to risk balance is judged to be unacceptable even after the effect of any appropriate action is taken into account, the medicinal product should be withdrawn from the market and the appropriate health-care professionals informed (see Section 1.6.4.). Such action may be taken voluntarily by marketing authorisation holders. It is recommended that any such intended action be discussed with all competent authorities concerned. All concerned competent authorities must be informed - well in advance of -any intended action.

For medicinal products authorised through national procedures, the competent authorities may (Article 116 - of Council Directive 2001/83/EC -) suspend or revoke an authorisation where the product proves to be harmful under normal conditions of use, in order to protect public health

Where a Member State considers that a marketing authorisation should be withdrawn as a result of the evaluation of -pharmacovigilance data, it is required to forthwith inform the-Agency , the Member State and the marketing authorisation of the medicinal product provided the Agency, the Commission and the other Member States - informed at the latest n the following day.- -

If the interests of the Community are involved, the competent authority of a Member State, the European Commission or the marketing authorisation holder may refer the matter to the CPMP for an Opinion according to Article – 31 of Council Directive 2001/83/EC -.

For medicinal products authorised through the mutual recognition and ex-concertation procedure, where a Member State considers the suspension or withdrawal of a product is necessary to protect public health, the matter will be referred to the CPMP for an Opinion (Article 36 and 37 - of Council Directive 2001/83/EC - respectively). - -In exceptional cases, were urgent action is essential to protect public health, until a definitive position is adopted, a Member State may suspend the marketing and

use of the medicinal product on its territory. The Member State is required to inform the Commission and the other Member States no later than the following working day of the reasons for its action. -

In the case of centrally authorised products Article 18 of Council Regulation 2309/93 states that where urgent action is essential to protect human or animal health or the environment, a member state may suspend the use on its territory of the medicinal product. It shall immediately inform the European Commission, the Agency secretariat and the other Member States no later than the following working day of the reasons for its action. The European Commission shall immediately consider the reason given by the member state and shall request the Opinion of the CPMP within a time limit, which it shall determine having regard to the urgency of the matter.

In the event that withdrawal of a product from the market seems likely, the marketing authorisation holder should be informed at an early stage of any possible intended action. In the case of medicinal products authorised through national procedures, it is the responsibility of the competent authorities in the Member States concerned to inform the holder of the marketing authorisation. For mutually recognised products, this task is normally undertaken by the reference member state. Where a product is authorised centrally, the Agency, in consultation with the Rapporteur, should inform and liaise with the marketing authorisation holder.

1.6.4 Communication

The content of the public statements, Dear Health Care Professional letters and other communication from the Marketing Authorisation Holder to health-care professionals, patients and the general public should always be agreed with the competent authorities and the time-scale for the distribution of that communication should be agreed with the relevant competent authorities as follows:

- For centrally authorised products with the rapporteur and the Agency secretariat:

The marketing authorisation holder should interact with the Member States to ensure that neither the translation of the agreed communication nor any local issues associated with the distribution of that communication will impact on the agreed time-scale. The marketing authorisation holder is responsible for keeping the rapporteur and the Agency secretariat informed of any issue which may affect the implementation of the agreed time-scale (see also Chapter 2.2.1 on *Conduct of Pharmacovigilance for Centrally Authorised Products*).

- For mutually recognised products with the reference Member State:

The marketing authorisation holder should interact with the concerned Member States to ensure that neither the translation of the agreed communication nor any local issues associated with the distribution of that communication will impact on the agreed time-scale. The marketing authorisation holder is responsible for keeping the reference Member State informed of any issue which may affect the implementation of the agreed time-scale (see also Chapter 2.2.3 on *Conduct of Pharmacovigilance for Medicinal Products Authorised through the Mutual Recognition Procedure*).

- For nationally authorised products with the competent authorities of all Member States in which the product is authorised.

The procedure of information distribution should ensure that information to health care professionals should not be disseminated later than information to patients and the general public.

Annexes

- 1. Member States Distribution Requirements for Periodic Safety Update Reports**
- 2. Periodic Safety Update Reports Tables 2.1 – 2.3**
- 3. Template for PSUR submission (EMEA)**

Annex 1

Member States Distribution Requirements

for

Periodic Safety Update Reports

Distribution Requirements for Periodic Safety Update Reports

Member State/EEA Country/Agency	Number of copies	Addressee(s)
Austria	2 (paper copies)	<ul style="list-style-type: none"> • Federal Ministry of Health and Women (1 copy) VIII/A/3 Pharmacovigilance Branch Radetzkystrasse 2 AT-1030 Vienna • Bundesinstitut für Arzneimittel (1 copy) Unit 2 Possingergasse 38 AT-1160 Vienna
Belgium	1 (CD-ROM+paper copy) 1 additional copy (CD-ROM+paper copy)	Federal Public Service Health, Food Chain Safety and Environment Directorate-General Public Health Protection: Medicinal Products Belgian Centre for Pharmacovigilance Boulevard Bischoffsheim 33, 1 st floor BE-1000 Bruxelles to attention of Rapporteur (if Belgian CPMP Delegate is Rapporteur)
Cyprus	1 (CD-ROM+paper copy)	Ministry of Health Pharmaceutical Services Drug Regulatory Sector CY-1475 Nicosia
Czech Republic	1 (CD-ROM+paper copy) Preference: CD-ROM-only PSUR in searchable format (pdf, html or MS Word)	Pharmacovigilance Unit State Institute for Drug Control Srobarova 48 CZ-100 41 Praha 10
Denmark	1	Danish Medicines Agency Medicines Control Division Axel Heides Gade 1 DK-2300 København S
Estonia	All authorisation types: 1 (CD-ROM+paper copy)	Bureau of Drug Information and Pharmacovigilance State Agency of Medicines 19 Ravila Str EE-50411 Tartu
Finland	<ul style="list-style-type: none"> • Centralised authorisations: 1 (CD-ROM or paper copy) 1 (additional) paper copy • National authorisations: 1 (CD-ROM or paper copy) • Mutually recognised authorisations: 1 (CD-ROM or paper copy) 1 (additional) paper copy 	<ul style="list-style-type: none"> • Attn.: Department of Safety and Drug Information National Agency for Medicines P.O. Box 55 FI-00301 Helsinki to attention of Rapporteur (if Finnish CPMP Delegate is Rapporteur) • Attn.: Department of Safety and Drug Information National Agency for Medicines P.O. Box 55 FI-00301 Helsinki if Finland is Reference Member State
France	2 (paper copies+CD-ROM)	Agence Française de Sécurité Sanitaire des Produits de Santé DEMEB / Unité AMM logistique 143-147, Boulevard Anatole France FR-93285 Saint-Denis Cedex

Member State/EEA Country/Agency	Number of copies	Addressee(s)
Germany	2 (paper copies)	<ul style="list-style-type: none"> • Bundesinstitut für Arzneimittel und Medizinprodukte (2 copies) Friedrich-Ebert-Allee 38 DE-53113 Bonn • For vaccines and products derived from blood according to Council Directive 89/381/EC, recombinant coagulation factors and monoclonal antibodies: Paul-Ehrlich-Institut (2 copies) Attn.: Referat A/2 Paul-Ehrlich-Strasse 51-59 DE-63225 Langen
Greece	1 (paper copy)	Ministry of Health, Welfare National Organization for Medicines Department of Pharmaceutical Studies Adverse Drug Reactions Section 284 Mesogion Av. GR-15562 Holargos
Hungary	1 (paper copy)	National Institute of Pharmacy Department of Pharmacovigilance Zrínyi u. 3 HU-1051 Budapest
Ireland	1 (CD-ROM and/or 1 paper copy) Centralised authorisations: CD-ROM & 1 (additional) paper copy* Mutually recognised authorisations: CD-ROM & 1 (additional) paper copy* National authorisations: CD-ROM & 1 (additional) paper copy	Receipts & Validation Unit Irish Medicines Board Earlsfort Centre Earlsfort Terrace IE-Dublin 2 *if Ireland is Rapporteur *if Ireland is Reference Member State always
Italy	1 (paper copy)	Agenzia Italiana del Farmaco Via di Sierra Nevada 60 IT-00144 Roma
Latvia	1 (CD-ROM+paper copy)	Human Medicines Registration Department State Agency of Medicines of Latvia 15, Jersikas St Riga LV-1003
Lithuania	Centralised authorisations: 1 CD-ROM only National and mutually recognised authorisations: 1 paper copy	State Medicines Control Agency Post-Authorisation Evaluation Unit Traku Street 14 LT-01132 Vilnius
Luxembourg	1 (paper copy)	Division de la Pharmacie et des Médicaments Villa Louvigny Allée Marconi LU-2120 Luxembourg

Member State/EEA Country/Agency	Number of copies	Addressee(s)
Malta	<u>National Authorisations:</u> 1 paper copy (CD-ROM+paper copy) <u>MRP authorisations:</u> <i>If Malta is RMS:</i> 1 paper copy (CD-ROM+paper copy) <i>If Malta is CMS:</i> 1 Electronic copy only on CD-ROM <u>Centralised authorisations:</u> <i>If Malta is RMS:</i> 1 paper copy (CD-ROM+paper copy) <i>If Malta is CMS:</i> 1 Electronic copy only on CD-ROM	<u>Six monthly and annual PSURs:</u> Attn: Pharmacovigilance Staff Post-Licensing Directorate Medicines Authority 198, Rue D'Argens MT-Gzira GZR 03 <u>First and subsequent renewal PSURs:</u> Post-Licensing Directorate Medicines Authority 198, Rue D'Argens MT-Gzira GZR 03 <u>Interim PSURs:</u> To the person from the Post-Licensing Directorate making the request.
Netherlands	1 (paper copy) 1 (additional) paper copy	Medicines Evaluation Board MEB Kalvermarkt 53 P.O. Box 16229 NL-2500 BE The Hague to attention of Rapporteur (if Dutch CPMP Delegate is Rapporteur)
Poland	1 (paper copy)	Office for Medicinal Products, Medical Devices and Biocides Pharmacovigilance Unit 41 Zabkowska Street PL-03 736 Warszawa
Portugal	1 (paper copy)	<u>Attn.:</u> Directorate of Human and Veterinary Medicines and Healthcare Products INFARMED Parque de Saúde de Lisboa Av. do Brasil, 53 PT-1749 – 004 Lisboa
Slovak Republic	1 (CD-ROM or paper copy)	State Institute for Drug Control Kvetná 11 SK-825 08 Bratislava 25
Slovenia	1 (CD-ROM+paper copy)	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia Mali trg 6 SI-1000 Ljubljana
Spain	2 (paper copies)	Agencia Española del Medicamento Calle Alcalá 56 ES-28071 Madrid
Sweden	1 (CD-ROM+paper copy) 2 additional copies (CD-ROM)	Medical Products Agency PO Box 26 SE-75103 Uppsala Attn.: CPMP Members (1 copy for each Member) Medical Products Agency PO Box 26 SE-75103 Uppsala

Member State/EEA Country/Agency	Number of copies	Addressee(s)
United Kingdom	1 (paper copy)	Medicines and Healthcare products Regulatory Agency PSUR Processing Room 13-1 1, Nine Elms Lane UK-London SW8 5NQ
Iceland	1 (CD-ROM (preferred) or paper copy)	Icelandic Medicines Control Agency Eidistorgi 13-15 P.O. Box 180 IS-172 Seltjarnarnes
Liechtenstein	1 (paper copy)	Kontrollstelle für Arzneimittel Amt für Lebensmittelkontrolle und Veterinärwesen Postplatz 2 LI-9494 Schaan
Norway	1 (paper copy)	Norwegian Medicines Agency Sven Oftedals vei 8 NO-0950 Oslo
EMEA Secretariat	1 paper copy and 1 paper copy or CD-ROM (only for centrally authorised products)	European Medicines Agency – EMEA Unit for the Post-Authorisation Evaluation of Medicines for Human Use Sector for Pharmacovigilance and Post-Authorisation Safety and Efficacy of Medicines 7 Westferry Circus Canary Wharf UK-London E14 4HB

Annex 2

Periodic Safety Update Reports Tables 2.1-2.3

Table 2.1:**Example of Presentation of Individual Case Histories**

(See 1.4.3.6. for full explanation)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH			
▪ Spontaneous ADR reports*	S	-	+
▪ Studies and compassionate use programmes	NS U	-	+
	NS L**	+	-
	SA	-	+
2. Literature	S	-	+
	NS U	-	+
3. Other sources			
▪ Regulatory authorities	S	-	+
▪ Contractual partners	S	+	-
▪ Registries	S	+	-

* Medically unconfirmed reports should be provided as a PSUR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.

** Line listing should be provided as PSUR addendum only on request by regulatory authorities.

S = serious; L = listed; A = attributable to drug by investigator or sponsor; NS = non-serious; U = unlisted

Table 2.2:

Example of Summary Tabulation**

Number of Reports by Term (Signs, Symptoms and Diagnoses) from Spontaneous (Medically Confirmed), Clinical Study and Literature Cases: All Serious Reactions

An * indicates an unlisted reaction

Body system/ADR term	Spontaneous/ Regulatory bodies	Clinical studies	Literature
CNS			
hallucinations*	2	0	0
etc.	-----	-----	-----
etc.			

Sub-total			
CV			
etc.			
etc.	-----	-----	-----

Sub-total			
Etc...			
TOTAL			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms should be given (e.g.: x-spontaneous/regulatory, y-clinical study, and z-literature cases)

** This table is only one example of different possible data presentations which are at the discretion of the MAH (e.g.: serious and non-serious in the same table or as separate tables, etc.)

Table 2.3:

Example of Line Listing

MAH NO	COUNTRY	SOURCE	AGE/ SEX	DAILY DOSE mg/day	DATE OF ONSET OF REACTION or time to onset	DATES OF TREATMENT or treatment duration	REACTION DESCRIPTION	OUTCOME	COMMENT

Annex 3

Template for PSUR submission (EMEA)

<Serial number> **PERIODIC SAFETY UPDATE REPORT**

for

ACTIVE SUBSTANCE(S): <Name(s)>

ATC CODE(S): <Code(s)>

MEDICINAL PRODUCTS COVERED:

Name of the Medicinal Product	Marketing Authorisation Number	Date of Authorisation (Underline EU Birth Date)	Marketing Authorisation Holder
< >	< >	< >	< >

AUTHORISATION PROCEDURE in the EU: <Centralised/MutualRecognition/National>

INTERNATIONAL BIRTH DATE (IBD): <Date>

PERIOD COVERED BY THIS REPORT:

from <Date> to <Date> (Data lock point)

DATE OF THIS REPORT:

<Date>

VOLUME: <Number>/ <Total number of volumes>

OTHER INFORMATION:

<Other identifying or clarifying information at the option of MAH>

DATA LOCK POINT OF NEXT REPORT:

<Date>

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

<Name>

<Address>

NAME AND CONTACT DETAILS OF THE QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE: <Signature>

LIST OF SERIAL NUMBERS

<Serial number>	<Period covered>

DISTRIBUTION LIST⁸

<Competent authority in the EU>	<Number of copies>

⁸ For medicinal products authorised through mutual recognition the Reference Member State and the Concerned Member States should be indicated.

2. Guidance and Procedures for Competent Authorities

**2.1 PROCEDURE FOR COMPETENT AUTHORITIES ON THE UNDERTAKING
OF PHARMACOVIGILANCE ACTIVITIES**

1. Introduction and Legal Basis

As described in Council Regulations No. 2309/93 (Articles 19-22), Commission Regulation 540/95 and Directive 2001/83/EC Articles 101 to 108 - each Member State must establish a national pharmacovigilance system for the collection and evaluation of information on medicinal products with particular reference to adverse reactions. Furthermore, Member States should take all appropriate measures to a) encourage physicians and other healthcare professionals to report suspected adverse reactions to the competent authorities and b) oblige marketing authorisation holders to systematically collect information on risks related to their medical products and to transmit those to the competent authorities.

The requirements and procedures involved in such a system are described in this chapter, which relates to medicinal products authorised in the community (using either national, centralised or mutual recognition procedures) and covers collection and evaluation of all information useful in the surveillance of medicinal products. This chapter should be read in association with the other relevant chapters on pharmacovigilance guidance included in this volume, in particular as described in chapters 2.2.A, *Conduct of Pharmacovigilance for Centrally Authorised Products*, chapter 2.2.3., *Conduct of Pharmacovigilance for Medicinal Products Authorised through the Mutual Recognition Procedure*, chapter 2.2.B, *Crisis Management Plan Regarding Centrally Authorised Products for Human Use* and Chapter 2.2.4. *Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in Human Pharmacovigilance*.

2. Establishment of a Pharmacovigilance System

Each Member State should have in place a system of drug surveillance, (hereafter referred to as "a national pharmacovigilance centre") for receipt and evaluation of all pharmacovigilance data within that Member State. Furthermore this centre must be in a position to handle these pharmacovigilance data in a way which is compatible with the procedures undertaken in the other Member States and the European Agency for the Evaluation of Medicinal Products (hereafter referred to as the "Agency") in order that pertinent data may be transferred between the Member States and the Agency.

The PhVWP has been given a mandate (Annex 2) to provide a forum for discussion, consensus development and co-ordination of pharmacovigilance issues at community level. Each Member State should ensure that it co-operates with the pharmacovigilance working party in order to fulfil its pharmacovigilance requirements at community level.

All Member States should co-operate with the WHO Collaborating Centre for International Drug Monitoring through their national pharmacovigilance centre, in keeping with the guidance on *Principles of Providing the World Health Organisation with Pharmacovigilance Information*, Part 1, chapter 2.6 of this volume.

3. Management of Pharmacovigilance Data

This section deals with the following procedures:

1. Management of spontaneous reporting programmes.
2. Management of company derived pharmacovigilance data.
3. Management of pharmacovigilance data from other sources.
4. Procedures for communications and evaluation of pharmacovigilance issues within the EU.

3.1 Spontaneous Reporting Systems

3.1.1 Introduction

Each Member State should have in place a system for the collection of spontaneous suspected adverse reaction reports from health care professionals (e.g. free postal or telephone system), and marketing authorisation holders (hereafter referred to as *MA holders*), see also section 3.2. Each pharmacovigilance centre must liaise with the healthcare professionals to increase the awareness of the reporting system, stressing its importance and encouraging reporting (e.g. by the provision of a user-friendly system of reporting and provision of feedback after each report as appropriate).

Member States should interact with doctors and other healthcare professionals to ensure adequate reporting of adverse reactions to the competent authorities. To this end, it is desirable that each Member State should ensure the following:

- that reporting of adverse reactions to the designated centre is made as simple as possible.
- that all adverse reactions are acknowledged where appropriate and further information is forwarded as requested.
- that regular contact is maintained between the pharmacovigilance centre and healthcare professionals for example by:
 - the publishing of regular adverse reaction bulletins,
 - the sending of "Dear Doctor" letters, where appropriate, (either by the competent authority and/or the MA holder),
 - the provision of requested information on a one-to-one basis where possible.

3.1.2 General Principles of Spontaneous Reporting Systems

The following recommendations concern the spontaneous reporting system procedure:

- A healthcare professional or marketing authorisation holder reports a suspected adverse drug reaction related to one or more medicinal products, to a national competent authority (pharmacovigilance centre). Reports are made in writing (e.g. using report forms), by telephone, electronically, or by any other approved way.
- Reports are collected and validated by the pharmacovigilance centre and are usually entered into a database. Serious reactions should be handled with the highest priority. The database is used to identify potential signals and analyse data in order to clarify risk factors, apparent changes in reporting profiles etc.
- Case reports must be made accessible to the Agency, to the competent authorities of other Member States, and to the concerned MA holders according to the criteria laid down in the Regulation and Directive, and described in the guidance on *Conduct of Pharmacovigilance for Centrally Authorised Products* (chapter 2.2.A) and *Conduct of Pharmacovigilance for Medicinal Products authorised through the Mutual Recognition Procedure* (chapter 2.2.3)

The following procedures relate to the competent authorities of Member States and are independent of the structure of the national pharmacovigilance system (centralised or regionalised). The procedures are divided into:

- case report collection and validation, case report storage,

- case report processing (evaluation and presentation for transmission), information feedback,
- Protection of data confidentiality and security,
 - data quality control and quality assurance.

3.1.3 Case Report Collection and Validation

This concerns the collection and validation of primary data i.e. the data transmitted from the reporter to the competent authority. For the validation and management of electronically transmitted reports, the specific operational procedure should be followed.

Case Report Collection

A pharmacovigilance spontaneous report concerns a single case; one patient, one identifiable reporter, one or more suspected reaction(s), and one or more suspect medicinal product(s). According to European Directives and Regulations, only serious cases reported by healthcare professionals will be received on an expedited basis.

Case Report Validation

If the initial report is oral or made by telephone, it should be confirmed in writing by a healthcare professional. When several suspected reactions to one or more suspected medicinal products occur in one patient, but are considered to be independent reactions, they should be treated as separate reports. If considered appropriate, especially in the case of serious or unexpected reactions, data in the report concerning the patient, the medicinal products taken, the reactions, including signs and symptoms and laboratory reports, and the dates should be confirmed by copies of most important and relevant original documents (e.g. hospital discharge forms, specialist reports, laboratory tests, prescriptions and post mortem reports etc.).

Completeness of reports should be evaluated according to data required, as set out in this Volume, Part 1, chapter 1, Notice to marketing authorisation holders or formats for data transmission (see "Individual Case Presentation for Transmission" Section 2.1.3.1.5. below).

Incomplete reports, especially when concerning serious or unexpected reactions, should be followed up promptly by obtaining further information from the initial reporter or other available sources. In some cases, it would also be appropriate to conduct further follow-up to obtain data on the long-term outcome of the reaction.

An adverse drug reaction report must contain the following information, as defined in Part 1, chapter 1, *Notice to marketing authorisation holders*:-

- an identifiable health-care professional,
- an identifiable patient,
- at least one suspected substance/medicinal product
- at least one suspected reaction.

This is the minimum information which allows the case to be entered onto a database and become available for signal generation in order to facilitate evaluation of cases. Every effort should be made to obtain complete information where appropriate.

A reaction is suspected if either the reporting healthcare professional or the MA holder believes there is a possible causal relationship between it and the medicinal product in question. If a reaction is spontaneously reported, this usually implies a positive judgement from the reporter unless the reporter explicitly gives a negative judgement on a causal relationship.

3.1.4 Case Report Storage

Initial raw data (paper based) must be stored and treated in the same way as other medical documents, with appropriate respect for confidentiality.

Case reports should be stored in a database by the pharmacovigilance centre. Data storage should ensure on-line accessibility of data at all reasonable times. Recommendations cover individual data entry, audit trail, and correct use of terminologies.

Data Entry

Conformity of stored data with the initial report should be ensured by a quality control procedure which provides for validation against the original data or images thereof.

Audit Trail

Storage should ensure traceability (audit trail) of all data entered or modified, including dates and sources of received data, dates and destinations of transmitted data.

Terminologies

The internationally agreed medical terminology (MedDRA) should be used. This is mandatory for single case reports received electronically from January 2002, and for regulatory reporting of all adverse drug reactions from January 2003. - - Reports entered into a database should be coded according to internationally accepted terminologies, (MedDRA, WHOART, ICD 9, ATC etc.) -which are compatible with the currently available version of MedDRA. Reaction terms should be entered as the closest term available in the terminology, and, if possible, also in the original reporter's words. Use of terminologies should be monitored and validated, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency verified.

3.1.5 Case Report Processing: Evaluation of Seriousness/Expectedness and Presentation for Transmission

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregate cases.

Evaluation of Data in Individual Cases

Data evaluation includes validation of the case report and determination of seriousness, and of expectedness of the suspected reaction. These terms (seriousness and expectedness) have specific meanings in the context of ADR report evaluation (see definitions). Evaluation of the probability of the causal relationship between medicinal products and the suspected reaction(s) is undertaken when considered appropriate. All methods used to evaluate these parameters should be documented. Evaluators should be trained in the methods used and their training verified.

Management of Duplicate Reports

Some cases, especially those which are serious, will probably be reported to competent authorities from more than one source or from a single source through more than one channel. The competent

authority should make every effort to ensure that case reports contain sufficient information to identify such duplicates, e.g. from patient / reporter initials (or names if allowed), addresses, date of birth, other dates. Databases should be reviewed regularly to identify duplicates in accordance with national competent authority and Agency procedures. After identification, duplicates should be flagged as such.

Identification of Individual Cases Requiring Specific Handling

Database management should ensure compliance with regulations, i.e. identification of cases flagged as serious or unexpected and of any other circumstance requiring specific handling or transmission. Procedures should be in place to ensure that cases previously identified and processed are identified as such and not processed or transmitted repeatedly as new cases (see audit trail 3.1.4 above).

Individual Case Presentation for Transmission

Cases sent to other competent authorities or MA holders should be transmitted according to the approved formats, as defined in Part 1, chapter 1.

Aggregate Case Processing and Alert Identification

Database management should enable users to identify case aggregates or trends indicating a signal. Once a possible signal has been identified, the possibility of a causal relationship should be assessed. In these cases, all adverse drug reaction reports should be classified according to national preferences or requirements, using nationally or internationally accepted methodologies. All reports fulfilling the minimum information requirement must be included in the overall analysis. Certain analyses (for example those concerning the role of risk factors) may be confined to cases where enough information is available, but it should be made clear that this is a subset of the data.

Aggregate case processing should allow case grouping by accepted terms (see Terminologies 3.1.4 above). The terminology used for case aggregation should be specified.

Competent authorities and MA holders should inform each other of identified signals which may impact on the risk-benefit profile of the medicinal product. The RAS/NUIS System should be used by competent authorities when applicable.

3.1.6 Information

Competent authorities should ensure that the reporter(s) of a case is informed of its receipt and provided with the allocated reference number if appropriate, and additional information, if requested.

Competent authorities should ensure that ADR data are transmitted to the MA holder as required.

Competent authorities should also ensure that healthcare professionals (and when necessary, treated patients) are informed of any significant changes where appropriate in the medicinal product information (SPC) and of any suspected hazards requiring vigilance.

Competent authorities should ensure that proper and timely information is provided to international bodies, in particular the World Health Organisation (WHO), in accordance with the guidance on *Principles of Providing the World Health Organisation with Pharmacovigilance Information*, Part 1, chapter 2.6 of this volume.

3.1.7 Quality Control and Quality Assurance

Quality control and quality assurance concern every step in the processes described above. Quality control and quality assurance should be ensured by competent authorities, which should devise and implement the necessary procedures.

3.1.8 Confidentiality and Security

Confidentiality of patients' records including their personal identity, if given, should always be maintained; where possible, identifiable personal details of reporting healthcare professionals should be kept in confidence, as appropriate and in keeping with national and European legislation.

At each stage of storage and processing of pharmacovigilance data, all care must be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the medical and administrative confidentiality of the data. This security extends to the complete data path. Case report information should only be provided in an anonymous form.

In addition, procedures should be taken to ensure security and noncorruption of data during data transfers.

3.2 Company Derived Pharmacovigilance Data

Introduction

According to the aforementioned legislation, the person responsible for placing any medicinal product on the market must ensure that he has an appropriate system of pharmacovigilance in place in order to ensure responsibility and liability for his product on the market and to ensure that appropriate action can be taken, when necessary. Guidance for MA holders on the implementation and practical procedures involved in complying with this legislation is laid out in Part 1, chapter 1.

Company derived pharmacovigilance will be in one of the following formats;

1. Individual adverse reaction reports
2. Periodic safety update reports (PSURs)
3. Company sponsored post-authorisation safety studies.

This section deals with the procedures, to be undertaken by the pharmacovigilance centre, for handling company-derived pharmacovigilance data.

3.2.1 Individual Adverse Reaction Reports

Each pharmacovigilance centre should ensure that all reports submitted by the MA holder conform with the requirements as laid out in Part 1, chapter 1, in order to ensure conformity of reporting of adverse reactions by MA holders in each Member State. Furthermore, each pharmacovigilance centre must ensure the validation and verification of all data included in these case reports as far as possible. Finally, each centre should ensure that these reports are followed up by the MA holder where appropriate, in order to improve the quality of data available and to facilitate causality assessment. Competent authorities should ensure that they have the capability to send and receive ADR reports electronically and to encourage MA holders to do so in a defined format.

3.2.2 Periodic Safety Update Reports (PSURs)

A periodic safety update report (PSUR) is intended to provide an update of the world-wide safety experience of a medicinal product to competent authorities at defined times post-authorisation. It is the responsibility of each pharmacovigilance centre to evaluate these reports for nationally authorised products as well as products authorised via the mutual recognition procedure, as appropriate.

For practical reasons, PSURs for products authorised via the mutual recognition procedure are evaluated by the Reference Member State (RMS). An assessment report is circulated by the RMS to all Member States (CMS) within 6 weeks of receipt of the PSUR.

In the case of nationally authorised products, any major action (e.g. variation, suspension or withdrawal of a marketing authorisation) considered necessary as a result of such evaluation should be notified to the Agency and the other Member States according to established procedures.

PSURs for centrally authorised products are evaluated by the rapporteur according to a timetable agreed by the CPMP. (See 3.4.4 below for procedures for medicinal products, authorised via the Centralised or Mutual Recognition Procedures).

3.2.3 Company Sponsored Post-Authorisation Safety Studies

These studies are normally conducted to assess the clinical safety of marketed medicines in routine clinical practice; they may be either hypothesis-generating or hypothesis-testing. MA holders proposing to perform such studies have been advised to discuss the draft protocol with the relevant regulatory authorities (see Part 1, chapter 1.5). Until Directive 2001/20/EC - of good clinical practice is implemented, national legislative requirements or guidelines will have been taken into account in those Member s-States where these exist).

The pharmacovigilance centre may review studies, which are taking place within its jurisdiction on a regular basis. All serious adverse reactions, resulting from these studies, should be submitted in the usual way by the MA holder/investigator and should be dealt with as outlined below.

On completion of each study, the final report should be evaluated and, in the case of nationally authorised medicinal products, all relevant data (e.g. showing significant changes in the frequency of known adverse reactions, the development of unexpected adverse reactions, new interactions etc.) should be incorporated into the Summary of Product Characteristics (SPC) and notified to the other EU Member States and the Agency. (See 3.4.3 below for procedures for medicinal products, authorised via the Centralised or Mutual Recognition procedures).

3.2.4 Communication between MA holders and Competent Authorities

Competent authorities should ensure that they communicate with MA holders according to existing legislation and guidelines (Directive 2001/83/EC-, Council Regulation 2309/93, Chapter 2.2.4 *Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in Pharmacovigilance*).

3.3 Pharmacovigilance Data from Other Sources

3.3.1 Intensive Monitoring Schemes

Intensive Monitoring is defined as a system of record collation in designated areas e.g. hospital units or by specific physicians in community practice. The competent authority may be involved in the drawing up of the protocol to undertake this collection of data or will be informed that such monitoring is taking place.

Furthermore, it may be considered appropriate in the authorisation of certain medicinal products to impose specific requirements in respect of reporting serious or unexpected reactions on the prescribing physician and to make these requirements a condition of use of the product under the terms of the marketing authorisation.

The relevant pharmacovigilance centre should ensure that data and reports are collected at agreed intervals and in an appropriate format.

3.3.2 Data on Misuse/Abuse of Drugs

Reports of suspected adverse reactions due to misuse and abuse of medicinal products (associated with therapeutic use), which are received by the pharmacovigilance centres (via spontaneous reports, company reports etc.) should be handled in the same way as for the other types of reactions.

3.3.3 Other Pharmacovigilance Data

These data include drug usage figures, published adverse reaction reports, pharmacoepidemiology studies conducted by organisations other than the MA holders, pre-clinical studies or significant quality data and reports on products not currently marketed in the Member States. These are important for determining frequency, occurrence of unexpected adverse reactions, new interactions etc. and overall risk/benefit analysis. In those cases (e.g. from pharmacoepidemiology studies) where significant data are received from these sources, these findings may be transmitted to the other Member States and the Agency, as part of a routine exchange of pharmacovigilance information, with a view to taking action as appropriate (see also Section 3.4.2).

3.4 Procedures for Communications and Evaluation of Pharmacovigilance Issues in the EU

Introduction

This section describes the procedures that should be implemented in order to improve the communication of pharmacovigilance information within the EU and to optimise human resources for identifying and evaluating pharmacovigilance signals.

The following areas will be discussed:

1. Transmission of Serious and other Adverse Reaction reports - general principles.
2. Procedures for transmission and management of detected signals.
3. Procedures for the final report evaluation of company sponsored post authorisation safety studies.
4. Procedures for the Evaluation of Periodic Safety Update Reports.
5. Special Safety Monitoring of Medicinal Products.
6. Technologies on data transmission to facilitate the implementation of the procedures conforming the new European Pharmacovigilance System.

3.4.1 Transmission of Serious Adverse Reaction Reports

All serious suspected reactions, occurring within the Member State and notified to the pharmacovigilance centre should be transmitted, according to the aforementioned legislation, to the MA holder and in the case of centrally authorised products to the Agency within 15 calendar days of their receipt by the pharmacovigilance centre.

In the case of centrally authorised medicinal products, it is the responsibility of the Agency to inform each Member State of serious reports received from other Member States. The method of transfer of information to be used should be such as to ensure that the information is transmitted within the time frame outlined in the guidance in chapter 2.2.A *Conduct of Pharmacovigilance for Centrally Authorised Products*. The data transmitted should be as complete as possible in order to facilitate assessment but it is not obligatory on the pharmacovigilance centre to have made a formal evaluation before this transmission. (See Rapid Alert 3.4.2 below).

Transmission of Other Adverse Reaction Reports

These include non-serious expected or unexpected adverse reaction reports which are received from all sources. Whenever appropriate, these data should be available for transmission, in summary form, to all relevant parties (MA holder, Member States, Agency), as outlined below (*See 3.4.2, "Non-urgent Exchange of Pharmacovigilance Information"*). Only data, evaluated by the pharmacovigilance centre are considered for transmission here.

3.4.2 Procedures for Transmission and Management of Detected Signals

Once a potentially serious safety problem (e.g. a series of unexpected or serious ADRs or an increase in the reporting rate of a known ADR report) for a certain product has been detected by a National Pharmacovigilance Centre, it should be transmitted to the other Member States and the Agency.

It is essential that there is communication of the problem at an early stage, before a national decision is taken.

There are two ways for communicating this kind of information, i.e. rapid alert and non-urgent exchange of information.

Rapid Alert

The purpose of the Rapid Alert System is to inform with the appropriate degree of urgency, the other Member States, the European Commission and the Agency on pharmacovigilance data of medicinal products. Each Member State is normally responsible for contacting the MA holder(s) in its Member State, when appropriate. Rapid Alerts concerning batch problems are not considered in these guidelines.

The criteria for sending a rapid alert is the concern about a change in the balance between risks and benefits that could lead to major changes in the authorisation such as urgent suspension or withdrawal of the marketing authorisation, the introduction of major contraindications, restrictions in the indications or availability of a product.

This should also include any such action initiated by the MA holder. See chapter 2.2.4 *Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in Pharmacovigilance*.

Non-urgent Exchange of Pharmacovigilance information

The criteria for a non-urgent exchange of pharmacovigilance information are:

- Requests for information from Member States, the European Commission and the Agency which may relate to a variety of safety issues which may require non-urgent actions or minor changes in the SPC.
- Provision of information between involved parties which does not require any response.

Prior to circulation of such information, Member States who consider there is a pharmacovigilance hazard should liaise with the Reference Member State in the case of product authorised via the Mutual Recognition Procedure or with the rapporteur and the Agency in the case of centrally authorised products.

Electronic transmission using the template available on the EudraNet homepage will be the preferred mode of information exchange. It is important that this exchange of pharmacovigilance information is focused on important issues so that involved parties do not become overloaded with information.

The procedure to be followed in this exchange of pharmacovigilance information is as follows:

- The information should be clearly labelled as non-urgent exchange of pharmacovigilance information.
- The reason for sending the information should be clearly stated.
- Any information required of recipients should be specified clearly.

Responses should only be sent to the originator of the request and the Agency, (for centrally authorised products). The originator of the request should collate the information received and send this to all Member States, only if the originator of the request wishes the issue to be considered at the pharmacovigilance working party. See chapter 2.2.4 *Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in Pharmacovigilance*.

3.4.3 Procedures for the Final Report Evaluation of Company-sponsored Post - authorisation Safety Studies

In accordance with the guidance for marketing authorisation holders on company-sponsored post-authorisation safety studies (Part 1, chapter 1, section 1.5), a final study report has to be sent by the MA Holder to the relevant Member States and in the case of centrally authorised products to the Agency.

In the case of studies conducted for nationally authorised medicinal products the relevant Member State(s) should be responsible for the evaluation of the final report.

In the case of medicinal products nationally authorised in several countries through the Mutual Recognition Procedure, and in order to optimise human resources, evaluation of the final report will normally be carried out by the Reference Member State.

In the case of medicinal products authorised through the Centralised Procedure, the Rapporteur who evaluated the product for its registration will normally assess the final report. A co-rapporteur may also be appointed by the CPMP.

All data from the study have to be evaluated and an assessment report will be elaborated as a result. This report has to be distributed among Member States/CPMP/Agency, as appropriate within three months of receipt of the formal report from the MA holder.

If any pharmacovigilance issue demanding action is identified in any phase of the evaluation, it will be communicated using the appropriate procedure as described above (3.4.2), including at least the minimum information(see glossary, Part 1, chapter 3) and the assessment report, (Annex 1).

3.4.4 Procedures for the Evaluation of Periodic Safety Update Reports (PSUR)

In accordance with the legislation, each Member State and the Agency will receive regular safety update reports from the MA holder.

In the case of medicinal products nationally authorised in several countries through the Mutual Recognition Procedure and with the aim of optimising efforts, the evaluation of these updates will normally be carried out by the Reference Member State within the agreed timetable outlined in chapter 2.2.3 *Conduct of Pharmacovigilance for Medicinal Product Authorised through the Mutual Recognition Procedure*.

In the case of medicinal products authorised through the Centralised Procedure the Rapporteur who evaluated the product for its registration will normally assess the Safety Update Reports within the agreed timetable described in the document *Conduct of Pharmacovigilance for Centrally Authorised Products*,chapter 2.2.1.

An assessment report will be elaborated and distributed by the Reference Member State to all Member State(s) within six weeks of receipt of the PSUR for medicinal products authorised via the mutual recognition procedure; or by the rapporteur to all Member States and the Agency according to the timetable adopted by the CPMP for medicinal products authorised via the Centralised Procedure.

3.4.5 Technologies on Data Transmission to Facilitate the Implementation of the Procedures Conforming the European Pharmacovigilance System

Compliance with the Directives and the development of the European Pharmacovigilance system has resulted in the development of a network (EudraNet) which enables electronic data transmission.

Standardisation of data elements for the electronic transmission of individual case safety reports (ICHE2B) have been agreed (see Part IV, chapter 3). The agreed (ICH M2) standardised electronic transmission format (SGML) will facilitate automatic data transfer between national databases, the Agency and the pharmaceutical industry as appropriate.

At this stage, four different levels of information can be identified:

1. Transmission of simple messages and free text document. This will cover the exchange of assessment reports (e.g. Annex 1 for drug safety problem assessment), meeting announcement and routine contacts between National Administrations, the Commission and the Agency.
2. Exchange of aggregate information such as the one described for the *Rapid Alert System (RAS) and Non-urgent Information System (NUIS) in-Pharmacovigilance* (Part -II, chapter 2.2.4).
3. Exchange of cumulative information (-
4. Exchange of single case data, via EudraVigilance that will enable expansion of the information whenever needed and the compliance with the Directives using one unique transmission format irrespective of the recipient system.

Apart from the facilities expressed, the electronic connection among every Member State and between Member States and the Agency provides other benefits such as automatic acknowledgement of when the information has arrived and of when this has been read by any of the recipients.

EudraNet provides all features of electronic transmission of information and security to ensure, if and when required, confidentiality, integrity, authentication and non-repudiation of the message

The functional aspects of exchange of information via EudraNet are described in the Standard Operating Procedures "EudraNet E-Mail Policy" (IT-SOP 9724.2.8) and "EudraNet Network Policy" (IT-SOP 9720.3.2). Member States are required to use their electronic mail boxes:

- Functional addresses: pharmacovigilance, information, RA
- Working group addresses: EudraVigilance

4. Changes to Marketing Authorisation

The competent authority in each Member State as part of its obligation to undertake ongoing evaluation of benefit/risk assessment must ensure that all pharmacovigilance data received and evaluated, as outlined above, are taken into account on an ongoing basis

In the case of nationally authorised medicinal products, where updated pharmacovigilance data are seen to adversely effect the benefit/risk profile of the medicinal product, the competent authority may wish to vary/withdraw the Marketing Authorisation or not to renew it as appropriate. Any significant

change to the MA status or SPC, undertaken nationally as a result of these pharmacovigilance data should be notified to the other Member States and the Agency.

The procedure to be followed for changes to MA status or SPC of medicinal products, authorised via the Mutual Recognition procedure is laid out in Commission Regulation EC 1084/2003(ex. 541/95) and the document on Pharmacovigilance for Mutually Recognised Products. It is the responsibility of the Reference Member State to co-ordinate the procedure. The changes are implemented simultaneously in all concerned Member States. In the case of centrally authorised medicinal products, changes in the SPC or MA status are undertaken according to Commission Regulation 1085/2003 EC (ex. 542/95) - and as outlined in the guidance in chapter 2.2.2.A, *Conduct of Pharmacovigilance for Centrally Authorised Products*.

As described in Commission Regulations 1084/2003 and 1085/2003 5(ex. 541/95 and 542/95), the MA holder may take provisional urgent safety restrictions in the event of risk to public health. These must be notified to the Agency and the Rapporteur (in the case of centrally authorised products) or the relevant competent authorities (in the case of products authorised in the mutual recognition procedure) within 24 hours before implementation. The Agency and national authorities have an opportunity to comment. The changes must be submitted as type II variations as quickly as possible after implementation. An urgent safety restriction for centrally authorised products may also be initiated by the European Commission or by an individual Member State for a product that has been authorised via the mutual recognition procedure or which has been the subject of referral. If the competent authorities have not raised any objections within 24 hours following receipt of that information, the urgent safety restriction shall be deemed to have been accepted. The corresponding variation application shall be submitted immediately. From 1 October 2003 not later than 15 days after the initiation of the urgent safety restriction. Under the terms of Articles 31, 36 and 37 of Directive 2001/83/EC and Article 18 of Council Regulation (EEC) 2309/93, a Member State, the Commission or MA holder may refer a pharmacovigilance matter to the CPMP whenever the interests of the Community are involved. With respect to Articles 31, 36 and 37 procedure to be followed is laid down in Article 36 of Directive 2001/83/EC.

These matters may be referred by the CPMP to the pharmacovigilance working party for consideration. The final decision reached will be binding on all concerned Member States.

ANNEX 1

Rapporteur's Pharmacovigilance Assessment Report

Format and content

1. Introduction

This section should clarify why the assessment has been undertaken.

2. Assessment of risks

This section will be specifically devoted to the safety concern under evaluation. It should encompass all relevant sources of information, including spontaneous reports, published literature, studies (pre-marketing clinical trials, postmarketing studies, epidemiological studies and intensive monitoring data), other data, e.g. mortality data to:

- a) characterise the problem (nature, severity, outcome);
- b) assess causal association;
- c) estimate frequency and comparative frequency, where possible;
- d) provide evidence of risk factors

3. Assessment of benefits

It should take into account the following, where known:

- a) the nature of the illnesses for which the medicine is indicated (e.g. fatal, life-threatening, disabling, self-limiting, etc.).
- b) absolute efficacy, as judged by placebo-controlled clinical trials.
- c) relative efficacy, as judged by studies comparing efficacy with that of appropriate alternative treatment(s)
- d) the characteristics of the population exposed to the medicine (e.g. elderly and hospitalised, young and healthy, etc.)

4. Overall risk-benefit evaluation

This section includes:

- a) an overall benefit/risk analysis in the context of the safety problem under assessment and relevant comparative safety with other medicinal products in the same class/or for the same therapeutic indication;
- b) discussion of the options for improving the risk-benefit ratio (see also this section in the guidelines to MA holder);
- c) recommended options for responding to the safety issue.

ANNEX 2

Mandate for a permanent CPMP working group on Pharmacovigilance (PhVWP) (1)

To provide a forum for dialogue and understanding between Member States and the Agency on Pharmacovigilance within the following framework:

A. ORGANISATIONAL MATTERS (Mandate and timeframe determined by CPMP)

1. Developing common principles and procedures for:
 - a) signal generation, investigation and evaluation
 - b) routine assessments e.g. periodic safety update reports
 - c) evaluation of safety issue(s) using a common assessment report.
2. Developing common principles and procedures for sharing information and communicating:
 - a) urgent issues (Rapid alert)
 - b) information requests on: - signals - other issues
 - c) "for information" issues.
3. Preparation of new and review of old guidelines on pharmacovigilance
4. Provide the focus and catalyst for:
 - a) training in pharmacovigilance assessment
 - b) the development of pharmacovigilance methods across the EU in liaison with EU pharmacovigilance research programmes
 - c) development of IT communication facilities (EUDRANET, IDA)
 - d) Support for international initiatives (ICH, WHO, CIOMS etc.)

B. PRODUCT RELATED ISSUES AT CPMP's REQUEST WITH PRECISE MANDATE AND IN DEFINED TIME FRAME (ad hoc expertise may be required on special topics e.g. blood products, vaccines etc.)

Evaluation of specific pharmacovigilance issues on the basis of an assessment report prepared by a rapporteur/co-rapporteur in order to reach consensus on:

- a) questions to be raised with MA holder(s) - preliminary discussions with MA holder(s) could be held by the group at the request of CPMP
- b) the conclusions of the scientific evaluation of the issue
- c) recommendation on options for actions for consideration by CPMP.

- (1) The mandate for the Pharmacovigilance working group is under revision and will be updated

C. OTHER INQUIRIES AT REQUEST OF NATIONAL AUTHORITIES (to be dealt with informally and communicated for information to CPMP)

1. Review of signals and issues identified by Member States in order to agree on a plan for investigation and assessment
2. Evaluation of specific pharmacovigilance issues on the basis of an assessment report prepared by national authorities in order to reach consensus wherever possible on:
 - a) the conclusions of the scientific evaluation
 - b) options for action

Constitution and Organisation of the group:

Membership: - Core group appointed by Member States - one delegate each reimbursed by Agency;

- one delegate from each of the three EFTA countries :Iceland, Norway, Liechtenstein
- ad hoc expertise when required
- Agency secretariat
- Observer from European Commission.
- Other observers in accordance with EMEA rules

Chairperson to be appointed by CPMP.

Frequency: every 1 to 2 months, for 2 days, one week in advance of CPMP meeting.

Meeting place Agency (EMEA), London without interpretation.

2.2.A CONDUCT OF PHARMACOVIGILANCE FOR CENTRALLY AUTHORISED PRODUCTS

1. Introduction

The objective of this paper is to describe a framework whereby all centrally authorised products are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken, when necessary, to protect public health.

The conduct of pharmacovigilance for centrally authorised products rests on obligations and activities placed, through legislation, on a number of parties, i.e. the Member States, the European Commission, the Agency and the Marketing Authorisation Holders (MAHs). In order to ensure that the obligations are met, it is necessary to clarify the respective responsibilities and roles of the various parties.

This chapter presents:

- principles relevant to the conduct of pharmacovigilance for centrally authorised products.
- the functions and procedures for conducting pharmacovigilance for these products.
- the specific roles of the Member States, the CPMP, the Pharmacovigilance Working Party (PhVWP), the (Co)-Rapporteur(s), the Agency secretariat, the MAHs and the European Commission, in carrying out functions and procedures for the conduct of pharmacovigilance for centrally authorised products.

2. Legal Framework

- The legal provisions regarding the conduct of pharmacovigilance for centrally authorised products are set out in Chapter 3 of Title II of Council Regulation (EEC) No. 2309/93 of 22 July 1993 and Council Regulation (EC) No 540/95 of 10 March 1995. In particular, Articles 19 to 26 of Chapter 3, of Council Regulation No. 2309/93, place obligations on the MAHs, the Member States and the Agency. The examination of variations to the terms of Marketing Authorisation and urgent safety restrictions is the subject of Commission Regulation (EC) 1085/2003(ex. 542/95)
- Obligations of the MAHs:

MAHs are obliged to report within 15 calendar days all suspected serious adverse drug reactions (ADRs) occurring within the EU to the Member States in whose territory the incident occurred (Article 22 § 1).

Furthermore, MAHs have to report all suspected serious unexpected ADRs from outside the EU to the Agency and the Member States within 15 calendar days (Article 22 § 1).

MAHs have to submit Periodic Safety Update Reports (PSURs) to the Agency and the Member States, at least every six months during the first 2 years following authorisation and once a year for the subsequent two years and at the time of application for the first renewal. Afterwards, in connection with subsequent renewals of the Marketing Authorisation, PSURs have to be submitted at 5-yearly intervals (Article 22 § 2).

- Obligations of the Member States:

In accordance with Article 23, Member States have to report all suspected serious ADRs occurring within their territory to the Agency within 15 calendar days.

- Obligations of the Agency:

Article 20 states that the Agency should receive all relevant information about suspected ADRs for Centrally Authorised Products. In accordance with Article 23, the Agency must inform the national pharmacovigilance systems of suspected serious ADRs occurring within a Member State.

- The legal provisions regarding supervision and sanctions for centrally authorised products are set out in Chapter 2 of Title II of Council Regulation (EEC) No. 2309/93 of 22 July 1993. In particular, Article 18 of this Chapter provides the basis and the procedures for adoption of Community Decisions following opinions by the CPMP on the measures necessary to ensure the safe and effective use of centrally authorised products.

3. Principles

The responsibilities and functions of the various partners involved in the Centralised Procedure have been well defined for the co-ordination and evaluation, of Centralised marketing authorisation applications and subsequent variation applications. This framework should also be applied to the conduct of pharmacovigilance for centrally authorised products. As a matter of principle, the handling and analysis of pharmacovigilance data should always be done in close co-operation between the (Co)-Rapporteur(s), the Agency secretariat and any Member State(s) who has identified a possible issue.

- The pre-authorisation Rapporteur should take the lead in pharmacovigilance, acting to evaluate all issues relevant to the centrally authorised product. However, there may be situations where the original Rapporteur is not able to fulfil the functions of such evaluation. In such cases the Co-Rapporteur could take this responsibility. If this is not possible, the CPMP would need to appoint another Rapporteur who could take on these responsibilities. In the particular case that one would be confronted with a class-related effect and different Rapporteurs were involved in the pre-authorisation assessment of the various centrally authorised products, the CPMP would need to appoint a “leading” Rapporteur.
- In view of the large number of issues to be handled in the post-authorisation period for centrally authorised products, the Rapporteur will have the responsibility for evaluating and reaching conclusions on these issues in accordance with an agreed timetable, and for determining the issues which need to be considered by PhVWP and CPMP, in close co-operation with the Agency secretariat.
- Information relevant to the risks and benefits of centrally authorised products need to be continuously collected in all Member States. Therefore, each Member State plays an important role in collecting information on ADRs and in identifying and evaluating possible alerts of drug safety hazards for centrally authorised products. The scientific expertise of the Member States will be utilised by the Rapporteurs in carrying out pharmacovigilance evaluations. The Rapporteur will generally use the expertise of the Member State from which he originates. However, if considered more appropriate the Rapporteur may work with another Member State.
- In accordance with current legislation the Agency secretariat should collect all information about serious suspected ADRs and distribute this information to the Member States. The role of the Agency secretariat, therefore, is one of continuous co-ordination of the Centralised Pharmacovigilance System. The Agency secretariat will ensure that MAHs for centrally authorised products adhere to the requirements for safety reporting in accordance with current legislation. Meetings, for MAHs, will be organised at the Agency at regular intervals in order to provide guidance on ADR reporting to the Agency. PhVWP will be informed of such meetings in advance and will be given the opportunity to participate.

- The Agency secretariat, in close co-operation with the Rapporteur, will inform the CPMP/PhVWP of any drug safety hazard concern wherever there is a need for discussion and subsequent action to be taken. It will, in agreement with the Rapporteur, participate in the identification of signals of possible unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects.
- The PhVWP provides a forum for discussion and evaluation of emerging data in order to reach recommendations for consideration by the CPMP. A Drug Monitor for centrally authorised products will be created to track safety issues and will be reviewed at each meeting of the PhVWP. In addition specific issues relating to PSURs, specific obligations, follow-up measures or the need for safety variations may be discussed by the PhVWP at the request of the Rapporteur. At the level of the PhVWP, emerging reports of unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects will be discussed. Furthermore, PSURs are routinely discussed at PhVWP level prior to their consideration by the CPMP.
- The primary responsibility of the MAHs is to assure the safety of their product. Therefore, the MAH is obliged to adhere to the legal provisions as to the spontaneous reporting of ADRs as well as to the submission of PSURs and other information. Furthermore, issues requiring clarification, further information or specific actions by the MAH need to be clearly presented to the MAH in writing. Such requirements of the MAH should be prepared in collaboration between the Rapporteur, the Agency secretariat and any Member State requesting further information, and endorsed where necessary by the CPMP. Meetings with the MAH should involve the Rapporteur, the Agency secretariat and others as considered necessary. Minutes of such meetings should be taken and distributed to attendees.

A summary of the role and responsibilities of each of the parties involved in the Centralised Pharmacovigilance System is provided in Annex 1.

4. Functions and Procedures

4.1 Reporting of ADRs for Centrally Authorised Products

4.1.1 Pre-Authorisation:

- Once an application for a marketing authorisation is submitted to the Agency, in the pre-authorisation period, information relevant to the benefit/risk evaluation may become available from the applicant, or Member States where the product is already in use on a compassionate basis, or from third countries where the product is already marketed. Since it is essential for this information to be included in the assessment carried out by the (Co)-Rapporteur(s) assessment teams, the applicant is responsible for informing immediately the Agency secretariat and the (Co)-Rapporteur(s).
- In the period between the CPMP reaching a final Opinion and the Commission's Decision there need to be procedures in place to deal with information relevant to the benefit/risk of centrally authorised products, which were not known at the time of the Opinion. It is essential for this information to be sent to the Agency and (Co)-Rapporteur(s) so that it can be rapidly evaluated to an agreed timetable and considered by the CPMP to assess what impact, if any, it may have on the Opinion. The Opinion may need to be amended as a consequence.

4.1.2 Post-Authorisation:

- Suspected ADRs related to centrally authorised products are reported directly by health care professionals, to each Member State. MAHs report serious suspected ADRs to the Member State in which the reactions occurred, within 15 calendar days of receipt. Each Member State

is responsible for following up the single case ADR reports it receives to obtain further information as necessary.

- The Member States should forward to the Agency secretariat serious suspected ADRs occurring within their territories.
- The Agency secretariat and all Member States should receive directly from the MAHs suspected serious and unexpected ADRs which occur in a country outside of the EU.
- The Agency secretariat should ensure that all relevant information about suspected serious unexpected ADRs from outside the EU are entered into the EudraVigilance database and Member States should ensure that data on suspected serious ADRs occurring in their territory are uploaded into the EudraVigilance database for retrieval e.g. by providing pre-defined reports or allowing for free queries on drug safety profiles. Until the EudraVigilance database is available, interim measures will be taken. Each Member State will transmit by E-mail to the Agency, on a two-weekly cycle, an ASCII file containing CIOMS II line-listings of all serious ADRs received by that Member State (national cases only) for centrally authorised products.

4.1.3 Distribution of Information

- Until the EudraVigilance database is implemented, the Agency secretariat within 24 hours of receipt of ADR line-listings from Member States, will compile a complete line-listing of EU ADRs for each centrally authorised product and distributed to the relevant Rapporteur and all Member States. A complete line-listing of EU and non-EU ADRs will be circulated by the Agency secretariat to the CPMP, i.e. all Rapporteurs, at each meeting of the CPMP.
- If cases are considered to be of particular relevance, a Member State may send a complete report directly to the Rapporteur with a copy to the Agency secretariat.
- Once EudraVigilance is implemented, Member States should be able to access the database electronically to receive ADR data on centrally authorised products.

4.2 Monitoring and Control of Authorisation

4.2.1 Signal Generation:

- It is likely that many potential signals will emerge in the early stages of marketing and it will be important for these to be effectively evaluated.
- A signal of possible unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects may be identified by
 - the MAHs
 - the Rapporteur
 - the Member States
 - the Agency secretariat in agreement with the Rapporteur
- It is the responsibility of each member state to identify alerts from information arising in their territory. However, it will be important for the Rapporteur and the Agency secretariat to have the totality of information on serious ADRs occurring inside and outside the EU in order to have an overall view of the experience gathered with the concerned centrally authorised product.

- As a matter of routine, the Rapporteur should continually evaluate line-listings of ADRs, in the context of information already available on the product, to determine the emerging ADR profile. Additional information should be requested from the MAH and Member States, as necessary, in liaison with the Agency secretariat.
- When a Member State other than the Rapporteur wishes to request information from the marketing authorisation holder (apart from routine follow-up of cases occurring on their own territory), for the purposes of signal generation, the request should be copied to the Rapporteur and the Agency secretariat.
- Member States will inform the Rapporteur(s) and the Agency when performing class-reviews of safety issues which include centrally authorised products.
- The Pharmacovigilance Working Party should regularly review the emerging safety issues which will be tracked through the Drug Monitor.

4.2.2 Risk Evaluation

- As signals of possible unexpected hazards or changes in the severity, characteristics or frequency of expected adverse effects may emerge from many different sources of data (see above), the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal.
- Irrespective of the origin identifying the signal, a risk evaluation should be carried out by
 - the Rapporteur, or
 - the Member State where a signal originated.
- The Rapporteur should work closely with the originator of the alert to evaluate the issues. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or originator Member State, or jointly.
- A Member State other than that of the Rapporteur should not start a full evaluation prior to having contacted the Agency secretariat and the Rapporteur, in order to prevent any unnecessary duplication of effort.

4.2.3 Periodic Safety Update Reports (PSURs)

- The MAH is required to provide PSURs to all the Member States and the Agency secretariat, at 6 monthly intervals post-marketing for the first 2 years, annually for the subsequent 2 years, at the time of application for the first renewal and thereafter 5 yearly at time of application for subsequent renewals. It is the responsibility of the Agency secretariat to ensure that the MAH meets these deadlines.
- The MAH should submit any consequential variations simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CPMP.
- It is the responsibility of the Rapporteur to evaluate and provide a report in accordance with the agreed timetable and to determine what issues if any need to be referred to the PhVWP and CPMP.

- Actions required following the evaluation of a PSUR will be determined by the Rapporteur and the MAH will be informed by the Agency secretariat, after agreement by the CPMP.
- Where changes to the Marketing Authorisation are required, the CPMP will adopt an Opinion which will be forwarded to the Commission for preparation of a Decision.

4.2.4 Post Authorisation Studies, world literature and other information

- Final and interim reports of MAH sponsored post authorisation studies and any other studies, and other relevant information, may emerge from the MAH, the Member States or other countries at times in between periodic safety updates.
- The Rapporteur should receive and assess any relevant information and provide an assessment report where necessary.
- As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CPMP.
- The actions required following an evaluation will be determined by the Rapporteur and the MAH will be informed by the Agency secretariat, after agreement by the CPMP.
- Where changes to the marketing authorisation are required, the CPMP will adopt an Opinion which will be forwarded to the Commission for preparation of a Decision.
- The MAH should submit any consequential variations simultaneously with the data, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CPMP.

4.2.5 Post Authorisation Commitments

- It is the responsibility of the Agency secretariat to ensure that the MAH meets the deadlines for the fulfilment of specific obligations and follow-up measures, and that the information provided is available to the Rapporteur and to the CPMP.
- The MAH should submit any consequential variations simultaneously with the requested information for the fulfilment of specific obligations/follow-up measures, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CPMP.
- For marketing authorisations granted under exceptional circumstances, specific obligations will be set out in Annex II.C of the CPMP Opinion. Specific obligations should be reviewed by the Rapporteur, at the interval indicated in the Marketing Authorisation and at the longest annually, and should be subsequently agreed by the CPMP. As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CPMP.
- For marketing authorisations granted under exceptional circumstances, the annual review will include a reassessment of the benefit/risk profile. The annual review will in all cases lead to the adoption of an Opinion which will be forwarded to the Commission for preparation of a Decision.
- For all marketing authorisations (whether or not the authorisation is granted under exceptional circumstances) follow-up measures may be established, which are annexed to the CPMP Assessment report. These will be reviewed by the Rapporteur, and will be considered by PhVWP and CPMP at the Rapporteur's request.

- Where changes to the marketing authorisation are required, the CPMP will adopt an Opinion which will be forwarded to the Commission for preparation of a Decision.
- In the case of non-fulfilment of specific obligations or follow-up measures, the CPMP will have to consider the possibility of recommending a variation, suspension, or withdrawal of the marketing authorisation, in accordance with the principles laid down in the document “Position Paper on how to proceed with specific obligations and follow-up measures for the management of the marketing authorisation”.

4.3 Proceedings in Case of Safety Concerns

4.3.1 Hazards in the pre-authorisation phase

- Following the receipt of single case reports or other information relevant to the benefit/risk of a product by the Agency secretariat and the (Co)-Rapporteur(s), the latter should assess these pharmacovigilance data. The outcome of the evaluation should be discussed at the CPMP for consideration in the Opinion.
- If pharmacovigilance findings emerge following an Opinion but prior to the Decision, a revised Opinion, if appropriate, should be immediately forwarded to the Commission to be taken into account before preparation of a Decision.

4.3.2 Hazards in the post-authorisation phase

A specific tracking system for safety issues relating to centrally authorised products, similar to the present drug monitor will be introduced and reviewed on a regular basis by the PhVWP at their meetings. This summary document will also record relevant actions that have emerged from periodic safety updates, specific obligations, follow-up measures and safety variations.

Following the generation of a signal the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal:

i) Non-urgent safety issues

- Potential concerns that do not fulfil the criteria for a Rapid Alert (see chapter 2.4) should be brought to the attention of the Rapporteur and the Agency secretariat only in the first instance.
- Further information may be requested from:
 - ⇒ other Member States by the originator of the issue using the Non-urgent information System, see Chapter 2.2.4
 - ⇒ the MAH by the Agency secretariat, in agreement with the originator of the issue and the Rapporteur.
- The Rapporteur should work closely with the originator of the alert to evaluate the issues.
- Following evaluation the need for further discussion at the PhVWP and CPMP will be determined by the Rapporteur, and any necessary actions will be agreed by CPMP.
- The Agency secretariat is responsible for transmitting the outcome of the evaluation to the MAH.

- However, if deemed necessary, the CPMP should formulate an Opinion on the pharmacovigilance data and forward it to the European Commission accordingly in order to take a Decision.
- These issues will be included in the Drug Monitor for centrally authorised products by the Agency secretariat.

ii) Urgent safety issues

- For urgent and serious issues the Rapid Alert System should be used by the Rapporteur, the Member States or the Agency secretariat when a signal is detected which leads to concern about the risk/benefit ratio of a centrally authorised product and which could lead to major changes for the status of approval. If it is the marketing authorisation holder who first identifies a potential urgent and serious issue, he needs to inform the Agency secretariat without delay.
- The Rapid Alert should be transmitted to the contact points of the Member States, the Agency, the European Commission and to the Rapporteur of the centrally authorised product which is the subject of the alert.
- The Agency secretariat, in agreement with the Rapporteur, should promptly start an inquiry and information exchange with the MAH(s).
- The Agency secretariat will co-ordinate the process.
- The Rapporteur should work closely with the originator of the alert to evaluate the issues. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or originator Member State, or jointly.
- Following risk evaluation a discussion should be held at the PhVWP and subsequently at the CPMP within a defined timeframe.
- Any resulting CPMP Opinion on the measures to ensure the safe and effective use of the centrally authorised product will be transmitted by the Agency secretariat to the European Commission, in order to take a Decision.

From 1 October 2003 where the Commission imposes USR to the holder, the holder shall be obliged to submit an application for a variation taking account of the safety restrictions imposed by the Commission, immediately and in any case no later than 15 days after the initiation of the USR. (Commission Regulation (EC) 1085/2003)

- In some cases immediate action is essential to protect public health. In such cases the basic steps outlined above need to be followed, but within a much shorter time-frame, with the involvement of PhVWP and CPMP at a much earlier stage, and with particular mechanisms in place to provide a CPMP Opinion and Commission Decision rapidly. Rapid actions will need to be co-ordinated across all Member States, however in some situations one or a number of Member States may consider it necessary to take immediate suspensive action before such co-ordinated action occurs.

⇒ Crisis Management:

- Following detection of an urgent safety hazard which could have a serious impact on public health, immediate action needs to be taken to evaluate and consider the options and timescale for action. An urgent safety restriction (USR) to be completed within 24 hours may be initiated by the marketing authorisation holder or the European

Commission if necessary. A Crisis Management Plan, agreed with the CPMP, has been implemented by the Agency secretariat in close consultation with the European Commission.

⇒ Action taken by a Member State:

- Upon detection of a safety hazard where urgent action is deemed essential to protect human health, a Member State may suspend the use of a medicinal product on its territory.
- The Member State must inform the Agency, the European Commission and other Member States no later than the following working day of the reasons for its action. The Rapid Alert System¹ should be used for this purpose.
- The European Commission will request the opinion of the Agency within a time frame which it shall determine depending on the urgency of the matter. In that respect two possible procedures can be envisaged for implementation by the Agency secretariat depending on the time frame:
 - the first procedure is described in the Crisis Management Plan
 - the second is the convening of an extraordinary CPMP by the Executive Director of the Agency, after consultation with the CPMP Chairperson, in order to provide the European Commission with a recommendation on the suspensive measures.

4.4 Statements to Health Professionals and the Public

Health professionals and, if considered appropriate, the public need to be informed about safety issues relevant to centrally authorised products, in addition to the information provided in product information. It is important that consistent information is provided in all Member States. If there is such a requirement the Rapporteur or the marketing authorisation holder in co-operation with the Rapporteur should propose the content of information for consideration by the PhVWP and subsequent discussion and adoption by the CPMP. The agreed information may be distributed in Member States by letters from the MAH or Member States authorities or through Member States' authorities' bulletins. In some cases co-ordinated press releases, in addition to the CPMP press release, may be necessary. The text and timing for release of such information should be agreed by all parties prior to their despatch. The marketing authorisation holder should notify the Agency without delay of any information he intends to make public at his own initiative, in order to facilitate consideration by the PhVWP and adoption by the CPMP as well as agreement about timing for release, in accordance with the degree of urgency.

Member States Member States Member States 4.5 Advertising (Subject to further discussion within the Pharmaceutical Committee)

Council Directive 2001/83/EC - lays down the legislative base for the control of advertising medicinal products. Because company marketing strategies for centrally authorised products may be similar across the EU, consideration should be given to what interactions should take place between Member States in the event of an important advertising concern with potential public health implications occurring with a centrally authorised product. The Agency and the Rapporteur should be informed by the Member States of such concerns. The PhVWP may be an appropriate forum to discuss such issues in order to ensure that when it is considered that a company is making misleading claims with safety implications in several Member States, consistent action is taken whenever possible. The CPMP should be informed subsequently.

Annex

Summary of the Role and the Responsibilities of all Partners involved in the Conduct of Pharmacovigilance for centrally authorised products

Marketing Authorisation Holder

- Establish and maintain a system, accessible at a single point in the EU, to collect, collate, and evaluate pharmacovigilance data
- Meet legal obligations for reporting suspected adverse drug reactions
- Meet legal obligations regarding the preparation and the submission of PSURs
- Respond fully to requests from authorities for additional information necessary for the evaluation of the benefits and risks of a medicinal product
- Ensure the Marketing Authorisation is maintained and reflects the latest information
- To submit an application for variation following an USR

Member States

- Have in place national pharmacovigilance systems
- Inform the European Commission, the CPMP, the Agency, the Member States and the MAHs of any relevant actions
- Collect and collate risk/benefit data
- Provide serious ADRs which have occurred in its territory to the Agency and the relevant MAH within 15 calendar days of receipt
- Identify and evaluate drug safety alerts and conduct risk/benefit evaluations
- Provide representation on CPMP, PhVWP and Rapporteurs/Co-Rapporteurs
- Implement Commission Decisions
- In case of urgent action to protect public health, suspend the use of the product in the Member State's territory and inform, in accordance with the legislation, the Agency and the European Commission of the basis for action

Agency secretariat

- Co-ordination of the Centralised Pharmacovigilance System
- Monitor the legal obligations of the MAHs
- Receipt of serious ADRs and provision to the Member States and the Rapporteur
- In agreement with the Rapporteur, identify signals of possible unexpected hazards or changes in expected

adverse effects

- In agreement with the Rapporteur, inform all involved parties of any safety hazard concern
- Co-ordination of the evaluation of data by the Rapporteurs and consideration by the CPMP to reach Opinions
- Communication of Opinions to the European Commission
- Communication with the MAH on all relevant issues in consultation with the Rapporteur
- Maintenance of the Crisis Management System for centrally authorised products

Rapporteur

- Responsible for evaluating all risk/benefit issues for centrally authorised products
- Regularly evaluate ADRs and other risk/benefit data on receipt, PSURs, company reports and variation applications to agreed timetables, obtaining additional information from the MAH and the Member States as necessary
- Provide risk-benefit assessment reports to agreed timetables for consideration by the PhVWP and CPMP as necessary, with proposals on appropriate remedial action

Pharmacovigilance Working Party

- Regularly review Drug Monitor of safety issues for centrally authorised products
- Discussion of emerging drug safety issues at the request of the Rapporteur
- Discussion of PSURs at the request of the Rapporteur
- Recommendations to the CPMP on risk/benefit evaluations and actions necessary to minimise risk and maximise benefit

CPMP

- Discussion of the risk/benefit on the basis of the Rapporteur's assessment report
- Formulation of Opinions

European Commission

- Competent Authority for centrally authorised products
- Formulation of Decisions
- Enforcement of legislative requirements and enforcement of the implementation of Decisions by Member States and MAHs

**2.2.B CRISIS MANAGEMENT PLAN REGARDING CENTRALLY
AUTHORISED PRODUCTS FOR HUMAN USE**

1. Introduction

This document outlines the principles underlying a Crisis Management Plan which allows rapid and efficient handling of crisis situations involving a centrally authorised product. In order to achieve this objective, it is necessary to plan and agree in advance with all the involved parties, how the crisis will be managed.

The Crisis Management Plan outlines the procedures to be followed in order to deal with the crisis and also highlights the management structures/systems to be set up. Once further developed, the Crisis Management Plan will be validated and tested with possible crisis scenarios and regularly updated.

2. Principles of the Crisis Management Plan

- The objective of the Crisis Management Plan is to define and implement a strategy for the rapid and efficient handling of crisis situations by the Agency secretariat in liaison with the CPMP, the Rapporteur, the competent authorities of the Member States, the European Commission and the Marketing and Manufacturing Authorisation Holder(s).
- A crisis is defined in the present document as an event which occurs when new information, which could have a serious impact on public health, is received for a centrally authorised product, and which requires immediate action.
- The new information can be related to pharmacovigilance issues (i.e. an urgent safety hazard), or quality issues (e.g. non-compliance with previous approved products specifications, product contamination,...). In some cases the new information can be related to both quality and safety concerns (for instance problems of viral contamination with biological products).
- Crises may be subdivided into those where, at the time the crisis is identified, the information has not become public, and those where it has. In the latter case, the handling of communications becomes crucial especially when public confidence is at risk.
- Sometimes a crisis may be triggered when there is no new information but media exposure leads to serious public concerns about a product. In this case implementation of the crisis management plan may be appropriate.
- There are two possible outcomes to the crisis:
 - urgent regulatory action is needed; in this case, a recommendation on the action to be taken has to be provided;
 - urgent regulatory action is not required; there is concern, but no evidence of a problem warranting regulatory action; in the latter, clarification of the fact that no urgent action is needed must be provided.

In both cases the basis of the conclusion should be documented.

- As a matter of principle, the handling of crises should always involve a close co-operation between all parties concerned, i.e. the competent authorities of the Member States, the European Commission, the Agency secretariat, the CPMP, the Rapporteur and the Marketing and Manufacturing Authorisation Holder(s). In accordance with the principles laid down in *chapter 2.2.A Conduct of Pharmacovigilance for Centrally Authorised Products*, the Rapporteur should have a key role when there is a safety issue, in close co-operation with the Agency secretariat. In case of quality related problems the supervisory Member State(s)

responsible for the inspection of the manufacturer or importer (for products manufactured outside the EEA) should have a leading role.

- The timeframe, during which a crisis should be dealt with, will depend upon the urgency of the matter. The proposed procedure should, however, be flexible enough to allow for immediate action to be taken (e.g. an urgent product recall), if considered necessary by the European Commission and/or the Member States. However, in the case of urgent action required to protect public health, Member States may need to take pre-emptive action in accordance with current Community legislation.

3. Crisis Management Structures

Three different management structures are foreseen, i.e.:

- a European Crisis Group;
- an Agency Crisis Team;
- an advisory network at the level of the Member States.

3.1 European Crisis Group

In order to deal successfully with a crisis, a European Crisis Group needs to be created. For logistical reasons, and rapid and efficient issue management, the core members of the European Crisis Group must be kept to a minimum. Again for logistical and time reasons, some meetings may need to take place without all members being present. Of course additional members and expertise may be co-opted into the European Crisis Group as need arises.

3.1.1 Composition of the European Crisis Group

- a. In case of safety concerns the core European Crisis Group comprises:
 - the Chairperson of the CPMP;
 - the Chairperson of the Pharmacovigilance Working Party;
 - the Rapporteur of the product concerned, supported by his/her scientific assessment team;
 - if appropriate, a representative of the Member State where a signal originated;
 - the Executive Director of the Agency, as well as the other members of the Agency Crisis Team (for further details, see Section 2.2.B.3.2.).
- b. In case of quality related problems the core European Crisis Group comprises:
 - a designated representative from the supervisory Member State responsible for the manufacturer or importer (participates by telephone/video conference if urgent);
 - if necessary, a designated representative, covering in particular inspections, from the Member State(s) where the problem occurred (participates by telephone/video conference if urgent);
 - the Executive Director of the Agency, as well as the other members of the Agency Crisis Team;

- the Chairperson of the CPMP and the Rapporteur of the product concerned, if appropriate (participates by telephone/video conference if urgent).

3.1.2 Role of the European Crisis Group

The primary role of the European Crisis Group is to deal with containing and controlling the situation.

This will be achieved by:

- confirming the crisis;
- managing the crisis situation:
 - a) defining a strategy to handle the crisis;
 - b) convening an exceptional CPMP meeting, if necessary, or referring the matter to the next CPMP meeting, in order to define what possible action should be taken considering the seriousness of the crisis;
 - c) ensuring that all interested parties are rapidly and fully informed.

The decision to convene the European Crisis Group will be taken by the Executive Director, in consultation with the CPMP Chairperson and the supervisory member state (the latter only in case of quality related problems).

3.2 Agency Crisis Team

The availability of an internal Agency crisis management structure involves the creation of an Agency Crisis Team, which should become operational within the shortest possible timeframe. It should be set up in such a way that it is also able to deal with crises arising during weekends or public holidays. The Agency Crisis Team should consist of an identified group of individuals. Amongst its members a public spokesperson needs to be appointed. His role is of utmost importance in order to prevent contradictory information going out.

3.2.1 Composition of the Agency Crisis Team

The Agency Crisis Team is normally chaired by the Executive Director, or, in his absence, a designated deputy.

The team has a core membership with optional/additional participants. The core members, in addition to the Executive Director, are:

- the Head of Unit; Post-authorisation evaluation of medicines for human use
- the Head of Unit; Veterinary medicines and inspectors
- the Head of Sector; Pharmacovigilance and post authorisation safety + efficacy medicine
- the Head of Sector; Inspection
- the Head of the Unit pre authorisation evaluation of medicine for human use;
- the Product team leader concerned;
- Other product team members as necessary involved.

Optional/additional participants may be co-opted as necessary; for example a legal administrator as well as support personnel (technical, secretarial and linguistic support) will be needed.

3.2.2 Role of the Agency Crisis Team

The role of this team consists of:

- co-ordinating all activities;
- acting at all stages in co-operation with the other participants of the European Crisis Group.

3.2.3 Tasks of the different Agency Crisis Team Core Members

The following Members have the following specific tasks:

The Executive Director (or, in his absence, a designated deputy):

- chair the Agency Crisis Team;
- act as a public spokesperson, when required;
- liaise with all parties concerned by the crisis;
- liaise with the European Commission;
- provide an appropriate level of information at all stages during the crisis.

3.2.3.1 In case of urgent safety concerns:

- a. the Head of the pharmacovigilance and post authorisation safety + efficacy medicine Sector:** act as an overall co-ordinator.

The co-ordinator is responsible for:

- as a precautionary measure, preparing safety profiles for all centrally authorised products;
- organising and co-ordinating the actions of the Agency Crisis Team Members;
- centralising all updated information related to the crisis;
- preparing all documents for external communication;
- informing the Executive Director and the Head of Unit, Post authorisation evaluation of medicines for human use of all developments.

- b. the Product team leader/other product team leader team members involved (or, in their absence, their alternate):**

- collect internal and external information on an ongoing basis in order to update, in liaison with the other product team members, the Safety Profiles routinely;
- collect internal and external information which has arisen in the circumstances of the crisis;
- write file notes on meetings and ensure that key action points and recommendations are documented and filed.

c. the Head of Unit, Post authorisation evaluation of medicines for human use:

- liaise with the Executive Director and the Chairperson of the CPMP to plan the public relations policy and ensure that at all times an appropriate public statement is available;
- provide all necessary scientific resources.

d. the Head of the unit pre authorisation evaluation of medicines for human use concerned:

- help and direct the activities of the Product team leader.

3.2.3.2 In case of quality issues:

a. The Head of the Inspection Sector: act as an overall co-ordinator.

The co-ordinator is responsible for:

- organising and co-ordinating the actions of the Agency Crisis Team Members;
- centralising all updated information related to the crisis;
- prepare all documents for external communication;
- informing the Executive Director and the Head of the Unit, veterinary medicines and inspections of all developments.

b. the Head of the Unit, veterinary medicines and inspections:

- liaise with the Executive Director to ensure that at all times an appropriate public statement is available;
- provide all necessary resources.

A list of all crisis contact points within the Agency is available.

3.3 Advisory network at the level of the Member States

A prerequisite in this respect is the availability of designated contact points within the Member States. This network should also foresee in the involvement of the national pharmacovigilance centres in case of safety hazards, and the involvement of the national services responsible for inspections of manufacturers of medicinal products in case of product defects.

A consolidated list of all contact points at the level of the Member States, implicated in the Crisis Management Plan, has been prepared. This list shall continuously be updated. It is the responsibility of the Member States to inform the Agency of any changes to be implemented.

4. Key Points of the Procedure to Be Followed

In addition to the management structures, management systems are put in place at the level of the Agency and the competent authorities of the Member States. They aim to meet the following objectives:

- To activate all available networks and to co-ordinate the different activities between the interested parties.

- To arrive at a common conclusion and - where regulatory action is considered necessary - an Opinion, as a basis for a common Decision, and to implement the Decision at the same moment in the whole European Union. This implies the availability of efficient immediate links with the Heads of National Agencies.
- To convey a unified message to the outside world. This implies efficient contacts with the European Commission and with the press officers available in the different Member States.

4.1 Handling of a crisis due to an urgent safety concern

Close co-operation between all the different parties involved should ensure the following:

- confirmation of the crisis;
- initiation, if considered necessary, of the crisis procedure;
- rapid scientific re-appraisal of the risk/benefit ratio of the product concerned;
- definition of strategy;
- recommendation on action or no action with documentation of the reasons for the recommendation;
- in case of regulatory action, monitoring of the enforcement in all Member States of the Decision taken by the European Commission;
- development of an action plan to monitor the sequelae.

A chart showing the decision flow is attached as Annex 1.

4.2 Handling of a crisis due to a quality related problem

The following steps need to be taken on receipt of a reported product defect or other quality related problems:

- confirmation of the crisis;
- initiation, if considered necessary, of the crisis procedure;
- evaluation of the seriousness of the defect using the classification in the document entitled “Community Procedures on Administrative Collaboration and Harmonisation of Inspections” (attached as Annex 2);
- establishment of the extent of the defect and hence the risk to public health;
- agreement on recommended action (i.e. agreed action, confirmation or modification of any action either planned or taken already) with the partners concerned and notification to the competent authorities of the Member States with a copy to the European Commission, and the Marketing and Manufacturing Authorisation Holders;
- monitoring of the progress and completion of the recommended action throughout the European Union.

A chart showing the decision flow is attached as Annex 3.

4.3 Public Relations

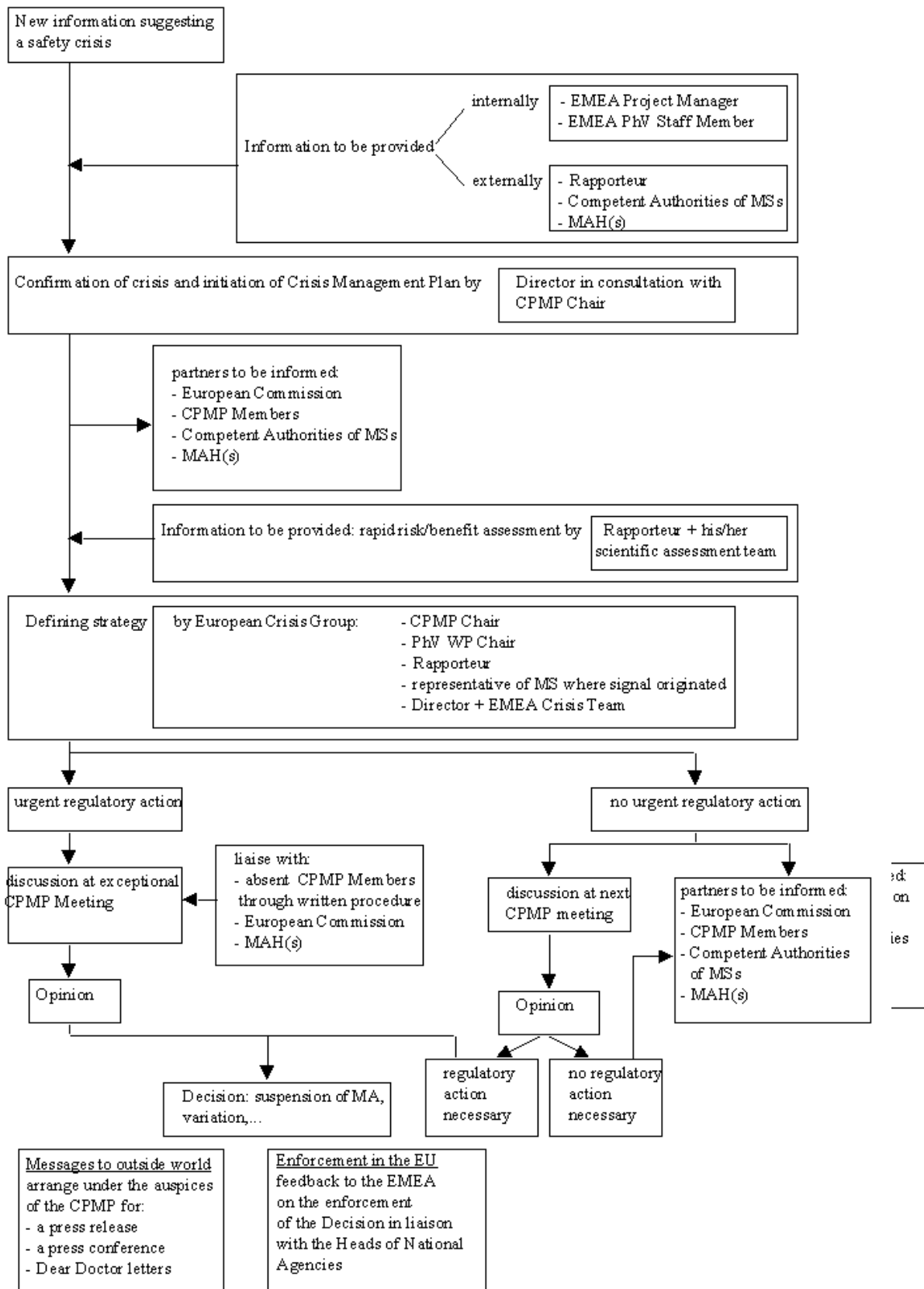
In all cases it is essential that public relations are handled sensitively and in a timely fashion. Failure to do so may mean that, however well the crisis is managed from a safety and regulatory perspective, public confidence will be lost and the image of the regulatory agencies will be damaged.

For this reason, the responsibility for press briefing and the preparation of statements is at the highest levels. Normally the Chairperson of the CPMP, the Executive Director of the Agency and the Head of either the Technical Co-ordination Unit (in case of quality related problems) or Human Unit (in case of safety concerns) will be responsible for public relations policy and the preparation of press releases.

A public spokesperson needs to be appointed from the above team. His role is of primary importance since the existence of one designated person should prevent contradictory information from entering the public domain.

The ideal is that press releases should be co-ordinated between the Member States, the Agency and the Marketing and Manufacturing Authorisation Holders. However in some situations, this ideal may not be met. In such cases, close co-operation between the Agency and the Member States should ensure that the messages coming from them are consistent.

Flow chart: Urgent Safety Concern



Annex 2

CLASSIFICATION OF BATCH RECALLS FOR QUALITY DEFECTS

CLASS 1 : Defects are potentially life-threatening or could cause a serious risk to health.

These must be notified through the Rapid Alert System in all cases.

Examples:

- 1.1: Wrong product (label and contents are different products)
- 1.2: Correct product but wrong strength, with serious medical consequences
- 1.3: Microbial contamination of sterile injectable or ophthalmic product
- 1.4: Chemical contamination with serious medical consequences
- 1.5: Mix-up of some products (rogues) with more than one container involved
- 1.6: Wrong active ingredient in a multi-component product, with serious medical consequences.

CLASS 2 : Defects could cause illness or mistreatment, but are not Class 1.

These should be notified through the Rapid Alert System only to Member States and MRA partners to which it is likely or known that the batch has been distributed (including parallel import/distribution).

Examples:

- 2.1: Mislabelling, e.g. wrong or missing text or figures
- 2.2: Missing or incorrect information (leaflets or inserts)
- 2.3: Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- 2.4: Chemical/physical contamination (significant impurities, cross-contamination, particulates)
- 2.5: Mix up of products in containers (rogues)
- 2.6: Non-compliance with specification (e.g. assay, stability, fill/weight)
- 2.7: Insecure closure with serious medical consequences (e.g. cytotoxics, child-resistant containers, potent products).

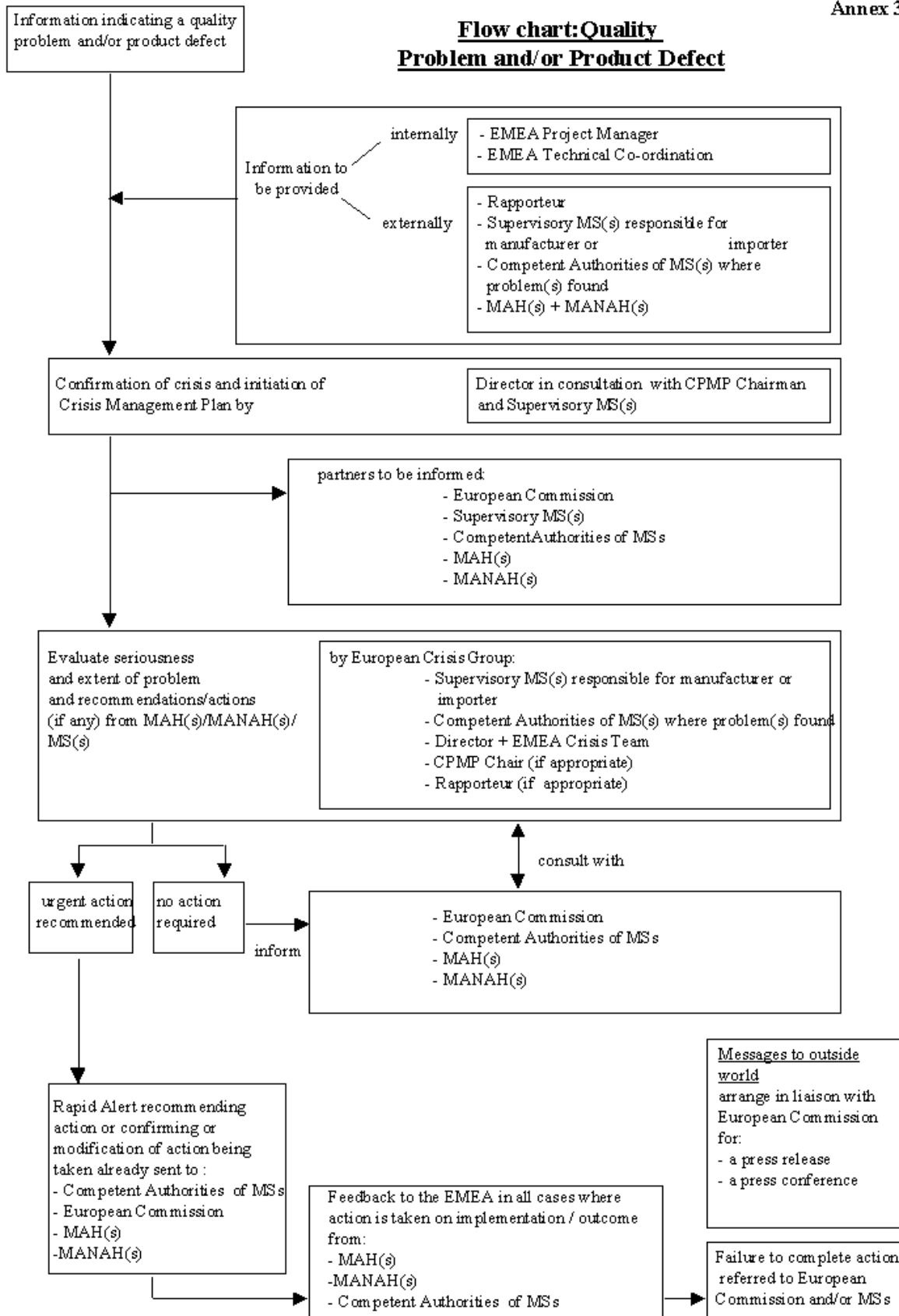
CLASS 3.:

Class 3 defects may not pose a significant hazard to health, but withdrawal may have been initiated for other reasons.

Examples:

- 3.1: Faulty packaging, e.g. wrong or missing batch number or expiry date
- 3.2: Faulty closure
- 3.3: Contamination, e.g. microbial spoilage, dirt or detritus, particulate matter

**Flow chart: Quality
Problem and/or Product Defect**



**2.3 CONDUCT OF PHARMACOVIGILANCE FOR MEDICINAL PRODUCTS
AUTHORISED THROUGH THE MUTUAL RECOGNITION PROCEDURE**

1. Introduction

The objective of this paper is to develop a framework whereby all medicinal products for human use which fall under the procedure of mutual recognition (MR) are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken, when necessary, to protect public health. Products covered by these procedures include those authorised through mutual recognition, ex-concertation products and those previously referred under Articles 30 and 31 of Council Directive 2001/83/EC -

The responsibility for the conduct of pharmacovigilance of any MR product rests with the competent authorities of all individual Member States of the European Union (MS) who have granted the authorisation. For products authorised by purely national procedures, a description of the conduct of pharmacovigilance is included in Part 2, chapter 2.1 *Procedure for competent authorities on the undertaking of pharmacovigilance activities*.

The process of MR is facilitated by the Mutual Recognition Facilitation Group (MRFG). It acts to support the development of consensus where differences of view arise so as to minimise the need for arbitration. For practical reasons, Member States have agreed that an analogous role for pharmacovigilance of MR products will be undertaken by the Pharmacovigilance Working Party (PhVWP). It should however be noted that this facilitation mechanism in no way changes the legal obligations for reporting of adverse reactions nor for referrals to the Committee for Proprietary Medicinal Products.

Because of the need to co-ordinate the process of pharmacovigilance and any consequential regulatory action across all relevant MS a standard operating procedure for the conduct of pharmacovigilance for MR products is necessary, this will reduce duplication of work and facilitate harmonisation between MS.

This paper presents:

- principles relevant to the conduct of pharmacovigilance for MR products
- a standing operating procedure for conducting pharmacovigilance for these products
- the specific roles of the different parties involved in carrying out these functions.

The procedures outlined in this document apply once a product has entered the MR procedure or falls within it by virtue of being part of the concertation procedure or following referral under Articles 30 and 31

2. Legal Framework

Council Directive -2001/83/EC sets the basis for the authorisation and variation of medicinal products through the MR procedure and for pharmacovigilance thereafter. Pharmacovigilance procedures and obligations of marketing authorisation holders (MAH), competent authorities and the European Agency for the Evaluation of Medicinal Products (the Agency), which includes the CPMP and the secretariat are outlined in this Volume. Commission Regulation (EC) No. 1084/2003 (ex 541/95) provides the legislative basis for variation of MR marketing authorisations including urgent safety restrictions.

3. Principles and Parties Involved

The responsibilities and functions of the various partners involved in the MR procedure are defined in the legislation for the handling of marketing authorisation and subsequent variation applications. Although there are no equivalent legislative procedures defined for the handling of pharmacovigilance

issues which arise for products which have been authorised by MR, Member States have agreed that similar principles should also be applied to the conduct of pharmacovigilance for MR products, with the Reference Member State (RMS) taking the lead in pharmacovigilance in close co-operation with Concerned Member States (CMS). Any reference to MS below should be taken to mean both the RMS and CMS. The role of the relevant parties is presented below:

3.1 Reference Member State (RMS)

For practical reasons, Member States have agreed that the RMS should be assigned responsibility for evaluating all pharmacovigilance issues relevant to a MR product, for providing assessment reports to the CMS to an agreed timetable and presenting the issues which need to be considered by the PhVWP. The RMS will be responsible for liaising with the MAH on all such matters. This includes an agreement on the format and the intervals at which all suspected serious ADRs occurring in the Community are made accessible to the RMS according to Article –104 of Directive 201/83/EC - - In cases where the original RMS expresses its inability to carry out these functions, another MS may be assigned to act as RMS. In situations where a class-related effect is identified for products with different RMS, a "lead" RMS may be appointed by agreement between the relevant RMS to take forward evaluation of the class-related effect.

3.2 Concerned Member States (CMS)

Competent authorities of all CMS have a responsibility to continuously collect information on ADRs and play an important role in identifying and evaluating possible alerts of drug safety hazards for MR products. The CMS will work closely with RMS on such issues, and will respond to proposals from the RMS within the agreed timetable.

3.3 Competent Authorities

All competent authorities are responsible for ensuring implementation of regulatory action in their MS.

3.4 Pharmacovigilance Working Party (PhVWP)

The PhVWP facilitates co-ordination of pharmacovigilance of MR products across MS and the development of consensus on conclusions and proposed actions where differences arise between MS

The PhVWP will be the forum for discussing all pharmacovigilance issues relevant to MR products. Issues for discussion may be raised by the RMS or CMS. The present mandate of the PhVWP encompasses consideration of issues at the request of the CPMP and at the request of MS. These issues are handled as clearly defined and separate parts of the PhVWP agenda. (See Annex 2 to Chapter 2.2.A)

3.5 Mutual Recognition Facilitation Group (MRFG)

The MRFG will be kept closely informed on issues relevant to it e.g. variations for safety reasons by provision of the minutes of the PhVWP and the attendance of the PhVWP chairperson at the MRFG as necessary.

3.6 Agency Secretariat and CPMP

The CPMP becomes involved in issues relevant to MR products whenever there is a procedure according to Council Directive 2001/83/EC Article 29, 31 or 36 The Agency secretariat has accepted to (1) provide administrative support to the PhVWP, (2) co-ordinate all activities in the event of referral to the CPMP and (3) be kept informed according to Council Directive 2001/83/EC Articles 105 and 107 -

3.7 European Commission

The European Commission is the competent authority for the adoption of any Decisions relating to medicinal products which have been adopted as a result of referrals according to Article 32,33 and 34 of Council Directive 2001/83/EC-

3.8 Marketing Authorisation Holders (MAH)

The MAH is obliged to adhere to the legal requirements of pharmacovigilance (e.g.spontaneous reporting of ADRs, submission of PSURs and other information including post-authorisation safety studies) for MR products as for any other nationally authorised products This info should be provided to all Member States at the same time. Member States have agreed that the RMS will act as the primary liaison with the MAH, specifying issues requiring clarification, further information or specific actions by the MAH including reporting conditions for serious ADRs occurring in the Community. This will be clearly presented in writing to the MAH by the RMS working closely with CMS. Meetings with the MAH should involve the RMS, and any other CMS by request. The conclusions of such meetings should be distributed to the PhVWP members and members of the MRFG.

4. Functions and Procedures

4.A Reporting, Distribution and Evaluation of Information Relevant to Pharmacovigilance of MR Products

1. During the Process of Consideration of a MR Application

In the interim time between an application for a marketing authorisation through the MR procedure and completion of this process, information relevant to the safety of the product may become available from the applicant, or MS or third countries where the product is already marketed. Since it is essential for this information to be included in the risk/benefit evaluation, the applicant is responsible for immediately informing the RMS and the other CMS. The RMS will assess whether this new information alters the overall assessment, circulating an amended assessment report as necessary.

2. After Completion of the MR Authorisation

2.1 Spontaneous single case reports

All MS competent authorities have spontaneous ADR reporting schemes whereby health-care professionals and MAH report suspected ADRs to medicinal products. Directive 2001/83/EC lays down specific obligations on MS competent authorities and MAH on the expedited reporting of suspected ADRs. MS are responsible for collecting, collating and evaluating reports occurring in their respective territory. Member States-

In accordance with Article 104 -of Directive 2001/83/EC -, for products which have been the subject of a mutual recognition or referral procedure, the MAH should additionally provide these reports to the RMS.

The MAH should report, on a expedited basis, all suspected serious unexpected adverse reactions occurring in the territory of a non-EEA country and brought to the MAH's attention by a health-care professional in such a way as to be available to the Agency should be made electronically using the data processing network foreseen in Article 105 of Directive 2001/83/EC. Reports from outside the EEA are required to be sent to all CMS, although the responsibility to collate and evaluate these reports has been assigned to the RMS by the Member States.

2.2 Periodic Safety Update Reports (PSURs) and other relevant post-authorisation information

The MAH is required to provide all competent authorities with PSURs and relevant safety information from post-authorisation commitments, post-authorisation studies, world literature, or other sources as outlined in the Directive –2001/83/EC and guidance for MAH. Any consequential variation should be submitted by the MAH at the same time. The RMS have agreed to evaluate the information, to identify any possible hazard, and to circulate an assessment report to the CMS within 6 weeks of receipt. CMS should respond within 3 weeks of receipt of the RMS assessment report. This assessment report will, if requested by the RMS or CMS, be discussed at a PhVWP meeting.

2.3 Signal generation

It is possible that potential signals will emerge in the early stages of the marketing of a MR product especially for a new active substance. It will be important for these signals to be evaluated effectively. A signal of possible unexpected ADRs or changes in severity, characteristics or frequency of expected ADRs may be identified from many different sources of information by the MAH, the RMS, or any CMS.

It is the responsibility of each MS to identify alerts from information arising in its territory. It will also be important for the RMS to have the totality of information in order to have an overall view of the experience gathered in relation to the concerned MR product. Additional information requested should be provided to all CMS.

As a matter of routine, the RMS should continually evaluate all newly submitted information in the context of information already available on the product, to determine the emerging ADR profile. The RMS should specify reporting conditions and request additional information from the MAH and CMS, as necessary. The PhVWP should regularly review emerging safety issues.

2.4 Risk evaluation

-

As signals of possible unexpected hazards or changes in the severity, characteristics or frequency of expected ADRs emerge, the relevant information needs to be brought together for effective evaluation over a timescale appropriate to the importance and likely impact of the signal.

Any risk evaluation prompted by a signal should normally be carried out by the RMS unless other arrangements are agreed with another MS e.g. the CMS where the original signal was identified. The RMS should in any case work closely with the originator of the alert. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the RMS or the originator MS, or jointly. Assessment reports may be discussed at the PhVWP as necessary on request of the RMS or CMS.

A MS other than the RMS should not start a full evaluation prior to having contacted the RMS, in order to prevent any unnecessary duplication of effort.

2.5 Tracking of pharmacovigilance issues

A tracking system for pharmacovigilance issues relevant to MR products is set up - The "MR Drug Monitor". record actions that arise from investigated signals, PSURs, specific obligations and follow-up measures and is reviewed at each PhVWP. The RMS for a particular product has agreed to be responsible for ensuring the monitor is fully up-to-date for that product and providing the relevant information to the Agency secretariat.

4.B Proceedings in Case of Safety Concerns

1. Hazards During the Ongoing MR Process

If, in the course of the MR process and following the assessment of all information relevant to the safety of a product, the RMS considers that a significant risk has emerged to change the benefit/risk balance, the outcome of the evaluation should be discussed at the PhVWP and be taken into account in any ongoing MR procedure within the MRFG.

2. Hazards after MR Authorisation

2.1 Non-urgent safety issues

Potential concerns that do not fulfil the criteria for a Rapid Alert should be brought to the attention of the RMS. The RMS may request further information from the CMS or the MAH. The RMS should work closely with the MS who identified the issue to evaluate the matter. Agreement needs to be reached in each case on the responsibility of evaluation of the issue by RMS or originating CMS, or jointly. Following evaluation, the need for further discussion at the PhVWP will be at the request of the RMS or CMS.

2.2 Urgent safety issues

For urgent issues the Rapid Alert System should be used by the RMS or the other MS when a signal is detected which leads to concern about the risk/benefit of a MR product and which could lead to major changes in the status of that authorisation. The Rapid Alert should be transmitted to the contact points of the RMS, the CMS, the European Commission and the Agency secretariat. The MAH should also be informed. The RMS should work closely with the originator of the alert to evaluate the matter. Agreement needs to be reached in each case on the responsibility for the management of the alert and the risk/benefit assessment report, by the RMS or originator CMS, or jointly. They will also decide which additional information is to be requested from the MAH and CMS. Following risk evaluation a discussion should be held at the PhVWP aimed at reaching agreement between RMS and CMS. In cases of particular urgency a special meeting of the PhVWP may need to be set up. Any MS may initiate immediate suspension of the marketing authorisation if considered necessary (see 3.2 below).

3. Actions Consequential to Safety Concerns

Issues are likely to emerge from the many sources of information considered above which warrant amendment to the conditions of the marketing authorisation, usually through the process of variation. In the case of serious risk, which is considered to outweigh the benefit of a product, there may be a need to withdraw the product from the market. Such actions may be taken voluntarily by MAH or compulsorily by competent authorities.

3.1 Action by the marketing authorisation holder

Variations of the marketing authorisation submitted by the MAH because of safety concerns should be handled through the variation procedures for MR products with the RMS evaluating the variation and circulating an assessment report to the CMS within the normal timescale.

For urgent safety issues, the MAH may submit an urgent safety restriction (USR). From 1 October 2003 the corresponding variation shall be submitted immediately and in any case later than 15 days after the initiation of the urgent safety restriction..

In the case of a MAH wishing to withdraw its marketing authorisation, action needs to be co-ordinated across the CMS by the RMS, including communication to health-care professionals. It is recommended that any such intended action be discussed at an early stage with all competent authorities concerned. In addition, all concerned competent authorities must be informed well in advance of any action taken.

3.2 Action by the Competent Authorities

If following risk evaluation by the RMS, it is considered that action is necessary to vary the terms of, or to suspend or withdraw the marketing authorisation of a medicinal product, the RMS should inform the CMS.

Where possible, in order to ensure a co-ordinated approach, efforts should be made to reach a consensus on the proposed action to be taken, through discussion within the PhVWP.

Where appropriate, the RMS should communicate with the MAH on the reasons for the conclusions reached by the MS and the action that should be taken by the MAH. If the MAH does not voluntarily vary, withdraw or suspend the MA, a referral according to Articles 36 or 37 -, 31- to the CPMP is necessary. In these cases, reference should be made to the SOP on referrals in accordance with the provisions of Council Directive 2001/83/EC - in the case of safety concerns related to medicinal products marketed in the European Union. The resulting CPMP Opinion will be followed by a single Decision of the European Commission binding on all MS.

In urgent cases, any MS may initiate immediate suspension of the marketing authorisation of a medicinal product informing all MS, the European Commission and the Agency secretariat within 24 hours. Such action should preferably be taken in all MS in a co-ordinated manner facilitated by a proposal from the PhVWP to the competent authorities of MS.

3.3 Communication to health-care professionals and the public

Health-care professionals, and if considered appropriate, the public may need to be informed about safety issues related to MR products. It is important that consistent information is provided in all MS.

In such cases, the RMS should propose the content of the information to be provided, and whenever possible, this should be agreed by the CMS and, if necessary considered by the PhVWP. There should be agreement whenever possible, on the method and timing of distribution of the information e.g. by letters from MAH or MS competent authorities, or through competent authorities' bulletins. Agreement should also be reached on the need and timing of press statements and the reaction to press enquiries.

**2.4 RAPID ALERT SYSTEM (RAS) AND NON-URGENT INFORMATION SYSTEM
IN PHARMACOVIGILANCE**

1. Introduction

During the marketing period of a medicinal product urgent measures to safeguard public health may be necessary. Within the European system of pharmacovigilance it is essential that information concerning safety hazards possibly resulting in major changes to the marketing authorisation status or the withdrawal of a product, is exchanged between the Member States, the European Agency for the Evaluation of Medicinal Products (Agency) and the European Commission (EC) with the appropriate degree of urgency.

An early exchange of information will enable the competent authorities of Member States to initiate data research and seek specialist expertise so that necessary decisions may be taken as soon as possible.

To support the rapid notification of safety concerns and the exchange of information required to take the necessary decisions, the competent authorities of Member States and the European Free Trade Association (EFTA) countries concerned (Iceland, Liechtenstein and Norway), the Agency and the EC operate the Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in accordance with the procedure laid down in the guidance in this chapter.

2. Purpose

The purpose of the Rapid Alert System (RAS) is to alert, with the appropriate degree of urgency, other Member States, EFTA countries concerned, the Agency and the European Commission about pharmacovigilance data related to medicinal products, which indicate that action could be needed urgently to protect public health. It is essential that the communication of such problems occurs at an early stage, normally before a decision is taken in a Member State.

The Non Urgent Information System (NUIS) is a procedure established to support the collection and exchange of pharmacovigilance information between the competent authorities of Member States, the EC and the Agency which does not fulfil the criteria for a Rapid Alert.

In both cases, the RAS and the NUIS, the issue may then be discussed in a broad manner

- at the Pharmacovigilance Working Party on the basis of the drug monitor and an assessment report if applicable,
- in the CPMP,
- or formalised within procedures laid down in Article 31 and 32 of Council Directive 2001/83/EC - or Article 18 of Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended.

3. Scope

The RAS should primarily be used in problems or concerns relating to safety and efficacy of medicinal products authorised according to

- Council Directive 2001/83/EC - - - nationally authorised medicinal products including those authorised through the mutual recognition procedure - and
- Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – centrally authorised medicinal products.

The system must not be saturated by the exchange of less urgent information. For this purpose the Non-Urgent Information-System should be used.

Rapid alerts regarding quality problems or concerning specific batches of medicinal product are not considered in this chapter. Those Rapid Alerts must be handled as laid down in the document *Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects* published in the *Compilation of Community procedures on administrative collaboration and harmonisation of inspections*, March 2000 as updated.

4. Criteria

4.1 Rapid Alert System (RAS)

The RAS should be used when a Member State has a concern about a change in the balance between risks and benefits of a medicinal product that could require major changes in the status of the marketing authorisation such as:

- the urgent variation, suspension or withdrawal of the marketing authorisation, the recall of the medicinal product from the market,
- changes in the Summary of Product Characteristics (SPC) such as⁹
 - the introduction of new contraindications,
 - the introduction of new warnings,
 - the reduction in the recommended dose,
 - the restriction in the indications,
 - the restriction in the availability of the medicinal product and
- the need to inform health care professionals or patients about an identified risk without delay.

Concerns about a change in the risk benefit balance of a medicinal product or an active ingredient authorised according to Council Directive 2001/83/EC - - Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended may be based on:

- a series of report(s) of unexpected and serious adverse drug reactions (ADRs),
- reports of an expected ADR which suggest greater severity or long-term sequelae than known or which identify new risk factors,
- significant increase in the reporting rate of expected serious ADRs,
- evidence from studies (clinical trials or epidemiological studies) indicative of unexpected risk or a change in frequency or severity of a known risk,
- knowledge that the efficacy of a medicinal product is not established as assumed to date,
- evidence that the risks of a particular product are greater than alternatives with similar efficacy.

⁹ With regard to Article -107 of Council Directive 2001/83/EC- these criteria define a significant variation of the SPC.

4.2 Non-Urgent Information System (NUIS)

For the exchange of potential concerns that do not fulfil the RAS criteria as defined above, the NUIS should be used. It refers e.g. to

- Pharmacovigilance data, which do not require immediate or urgent action and/or where additional information is required from other Member States to support the evaluation of a potential concern,
- Provision of pharmacovigilance information, which does not require a response.

5. Procedure

Normally the case relating to the suspicion or concern is formulated by one Member State after evaluation of the data available in that Member State or the receipt of any other relevant important information that should be shared with other Member States, the EFTA countries concerned, the Agency and the EC. This should also include any action initiated by the Marketing Authorisation Holder(s) (MAHs).

5.1 Sending a Rapid Alert or Non-Urgent Information

In accordance with Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended, Article 24, the Agency, in consultation with Member States and the European Commission, has set up a data-processing network (EudraNet) for the rapid transmission of data between the EU competent authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding medicinal products marketed in the Community.

Following the successful piloting between Member States, the EC and the Agency, the electronic submission shall replace the Telefax system used in past to exchange this kind of information. However, in case of urgency e.g. EudraNet access is not available or the network is down, the former Telefax system should be used as alternative. The electronic communication with partners that are not connected via EudraNet has to be performed in a way that guarantees security and confidentiality of the data exchanged.

The establishment of pre-defined data formats is essential to ensure the collection of similar data, aid in exchange of information among the Member States, and assist the common evaluation. Proposed forms are enclosed with the guidance in this chapter. Templates are available on the EudraNet homepage <http://eudranet.eudra.org/> and can be accessed via the established Pharmacovigilance domain.

To send the form, the established Rapid Alert (RA) and NUI (Non Urgent Information) address list (HUMAN RA + NUIS) and mailboxes should be used which refer to the contact points within the competent authorities of Member States, the Agency and the EC. The EudraNet E-mail policy IT-SOP 9724 in the latest version applies accordingly.

If using the RAS/NUIS the Member State should comply with the following rules:

- a) The template chosen must comply either with the Rapid Alert or the Non-Urgent Information System criteria.
- b) Clear and concise information on the reasons for the Rapid Alert/Non-Urgent Information should be provided so that there is no need for clarification in the first instance.
- c) The competent authority generating the Rapid Alert/Non-Urgent Information should transmit at least the minimum information listed in Annex I and template A.

- d) Any information required from recipients should be clearly specified.
- e) In the event a Telefax is sent it should be preferably typewritten; the size of the letters should be large enough to ensure that the text is satisfactory readable.
- f) Annexes to the RAS/NUIS, considered to give sufficient details where necessary, should also be transmitted electronically, if available. The format to be used is the one specified in the EudraNet E-mail policy IT-SOP 9724 in the latest version. In case, the annexes are not available electronically, the form should be completed including a reference that the referred annexes would be submitted separately via Telefax; the form should be sent via the defined address list to the dedicated mailboxes. A print out of this completed form should be attached to the faxed annexes.
- g) The Rapid Alert should be transmitted in case of a medicinal product authorised according to
- Council Directive 2001/83/EC - - - *nationally authorised medicinal products including those authorised through the mutual recognition procedure* - to the contact points of the Member States, the EFTA countries concerned, the Agency and the EC,
 - Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – *centrally authorised medicinal products* - to the contact points of the Member States, the EFTA countries concerned, the Agency, the EC and the Rapporteur.
 - The Rapid alert should in any case also be provided to the chairperson of the CPMP.
- h) Non-Urgent Information should be transmitted in case of a medicinal product authorised according to
- Council Directive 2001/83/EC- – nationally authorised medicinal products - to the contact points of the Member States, the EFTA countries concerned, the Agency and the EC,
 - Council Directive 2001/83/EC- medicinal products authorised nationally through the mutual recognition procedure - to the contact point of the RMS, all other Member States contact points, the EFTA countries concerned, the Agency and the EC,
 - Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – *centrally authorised medicinal products* - in the first instance only to the Agency and the Rapporteur. The originator of the issue and the Rapporteur may request further information from other Member States.
 - The Non-Urgent Information should in any case also be provided to the chairperson of the CPMP.
- i) If the fax is used it has to be transmitted to the established contact points as indicated above. A list of the fax numbers will be also accessible on the EudraNet homepage. Changes related to the fax numbers should be notified to the Agency, the EC and the contact points in Member States and the EFTA countries concerned, immediately.
- j) In case of urgency, when the Member State concerned has suspended the marketing authorisation of a medicinal product or has withdrawn the medicinal product from the market in order to protect public health, the Agency, the EC, all Member States and the EFTA countries concerned have to be informed at the latest on the following working day.

k) When a Rapid Alert is circulated

- Related to a medicinal product authorised according to Council Directive -2001/83/EC - - *nationally authorised medicinal products* - the initiating Member State should inform the MAHs concerned in his country adequately and promptly. Receiving Member States are responsible for informing MAH(s) in their own country. Information on the MAH(s) may be given via associations of the MA holders both in the sending and receiving Member State.
- Related to a medicinal products authorised according to Council Directive 2001/83/EC - - *medicinal products authorised nationally through the mutual recognition procedure* - the RMS should inform the MAH adequately and promptly.
- Related to a medicinal product authorised according to Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – *centrally authorised medicinal products* - the Agency secretariat in agreement with the Rapporteur will promptly start an inquiry and information exchange with MAH(s).

l) According to the chapter 2.2.6 on *Principles of Providing the World Health Organisation with Pharmacovigilance Information* (CPMP/PhVWP/053/98), Rapid Alerts will be sent for non-centrally authorised medicinal products by the Member States and for centrally authorised products by the Agency in agreement with the EC if definitive measures related to the marketing authorisations of medicinal products (restriction, variation, suspension, withdrawal) are implemented by the competent authority or if the rapid alert informs about a public statement (positive or negative) made by the competent authority.

5.2 Responses to a Rapid Alert or Non-Urgent Information

Responses to a specific Rapid Alert should be sent only to the originating Member State and the Agency no later than one week of receipt of the alert.

In case of a Non-Urgent Information requested answers should be provided to the originating Member State and the Agency within the time frame indicated by the originator.

The template (see template B) to be used is the "ANSWER TO RAPID ALERT/NON-URGENT INFORMATION". The information requested by the generating Member State should be provided.

The Agency will summarise the issues related to Rapid Alerts and Non-Urgent Information in the Drug Monitor, which will be discussed and updated at each meeting of the Pharmacovigilance Working Party.

5.3 Assessment of a Rapid Alert

An interim assessment report should be prepared within five weeks after transmission of the initial Rapid Alert

- for nationally authorised medicinal products, (according to Council Directive 2001/83/EC) - - - by the originating Member State taking into account all information received and collated from other Member States,
- for medicinal products authorised nationally through the mutual recognition procedure, (authorised according to Council Directive 2001/83/EC) - - - any risk evaluation should normally be carried out by the RMS unless other arrangements are agreed with Member States. In each case agreement needs to be reached on the responsibility for the management of the alert and the risk/benefit assessment by the RMS, or originator CMS, or jointly.

- for medicinal products authorised according to Council Regulation (EEC) No. 2309/93 of 22 July 1993 – centrally authorised medicinal products - the Rapporteur should work closely with the originator of the alert to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or the originating Member State, or jointly.

When the collated information provides evidence of a serious safety concern a full risk/benefit assessment report for consideration by the Pharmacovigilance Working Party should be prepared.

The assessment report should be sent to all competent authorities in Member States, the EFTA countries concerned, the Agency and the Commission and should be discussed at the next meeting of the Pharmacovigilance Working Party (PhVWP).

The assessment report should be distributed electronically using the defined H-Pharmacovigilance address list and the established mailboxes as indicated in the EudraNet E-mail policy in the latest version. The electronic communication with partners that are not connected via EudraNet has to be performed in a way that guarantees security and confidentiality of the data exchanged. Consideration will need to be given to whether the matter is of Community interest and should be referred under Article 31 and 32 of Council Directive 2001/83/EC.

5.4 Assessment of Non-Urgent Information

On the basis of the Drug Monitor the Pharmacovigilance Working Party will discuss all topics exchanged via the Non-Urgent Information System and will agree on a case to case basis how to process the issue. In the event the preparation of an assessment report is considered necessary the same assessment procedure applies as indicated for a Rapid Alert (Section 5.3).

Annex I

Information for transmission of information about detected signals

Minimum information that should be filled in every case

1. Identification

- Type of message categories: select Rapid Alert/Non-urgent Message
- Reference:
- From:
- To:
- Date:

2. Medicinal Product

- Brandname(s):
- Active substance(s): (INN)
- Status of the medicinal product
 - κ - Centrally Authorised Product,
 - τ - Nationally Authorised Product,
 - > - Mutual Recognition Product,
 - x - Product which has been subject to a referral process
- Pharmaceutical form and dosage (if appropriate):
- Marketing authorisation holder(s)
- Manufacturer (if essential)

3. Reason for Alert

- Source of information: Spontaneous reports/Post-Authorisation Study/Clinical Trial/Pre-clinical Study, others
- summarised evidence relevant to alert

4. Actions

- Action(s) proposed
- Action(s) taken (steps taken to collect more information at a national level and temporary steps taken to limit risks)

5. Information exchange

- Information required

Template A

Logo and name of the Competent Authority of the Member State/EMA

<RAPID ALERT/ NON-URGENT INFORMATION>		
IN		
PHARMACOVIGILANCE		
Reference:	N° of attachments:	Date:
FROM:		
TO: (ALL) MEMBER STATES EFTA countries concerned EMA EUROPEAN COMMISSION CHAIRPERSON-CPMP RAPPORTEUR (if applicable) RMS (if applicable)		

SUBJECT:

Please fill in the appropriate fields

Brandname(s)¹: <select K | t | > | x >

International Non-proprietary Name (INN) or Class¹: <select K | t | > | x >

Strength(s):

Pharmaceutical Form(s) and Dosage(s):

Route of Administration(s):

Therapeutic Classification (ATC code):

Marketing Authorisation Holder:

Indication(s):

REASONS FOR <ALERT / NON-URGENT INFORMATION>:

(Relevant Summarised Evidence)

(Text)

Source of Information:

Please select:

Spontaneous Reports

Post Marketing Study

Clinical Trial

Preclinical Study

Other (please indicate)

PROPOSED ACTION AND ACTION TAKEN:

(Text)

INFORMATION REQUESTED:

(Text)

ADDITIONAL INFORMATION:

(Text)

Please respond by --/--/--

Name of person responsible for sending message:

Template B

Logo and name of the Competent Authority of the Member State/EMA

ANSWER TO <RAPID ALERT / • NON-URGENT INFORMATION> IN PHARMACOVIGILANCE		
Reference:	N° of attachments:	Date:
FROM:		
IN ANSWER TO THE ORIGINAL MESSAGE FROM <MEMBER STATE> DATED --/--/--		
TO: (ALL) MEMBER STATES EFTA Countries concerned EMA EUROPEAN COMMISSION CHAIRPERSON CPMP RAPPORTEUR (if applicable) RMS (if applicable)		

Respond requested by originator for --/--/--

SUBJECT:

Please fill in the appropriate fields

Brandname(s)¹: <select K | t | > | x >

International Non-proprietary Name (INN) or Class¹: <select K | t | > | x >

Strength(s):

Pharmaceutical Form(s) and Dosage(s):

Route(s) of Administration:

Therapeutic Classification (ATC code):

Marketing Authorisation Holder:

Indication(s):

**ANSWER TO <RAPID ALERT / NON-URGENT
INFORMATION>:**

(Text)

PROPOSED ACTION AND ACTION TAKEN:

(Text)

ADDITIONAL INFORMATION:

(Text)

Name of person responsible for sending message:

**2.5 STANDARD OPERATING PROCEDURE (SOP) ON REFERRALS IN
ACCORDANCE WITH THE PROVISIONS OF COUNCIL DIRECTIVE
2001/83/EC IN THE CASE OF SAFETY CONCERNS RELATED TO MEDICINAL
PRODUCTS MARKETED IN THE EUROPEAN UNION**

1. Scope

Safety issues relating to medicinal products authorised in the European Union may be referred to the CPMP under various circumstances.

- **Safety referrals in relation to Centrally Authorised Medicinal Products**

Centrally authorised medicinal products which are referred to the Committee in accordance with the provisions of Article 18 of Council Regulation (EEC) No 2309/93 are already covered in Part 2, chapter 2.2.A *Conduct of pharmacovigilance for Centrally Authorised Products*".

- **Safety referrals in relation to Non-Centrally Authorised Medicinal Products**

In relation to non-centrally authorised medicinal products, safety referrals can be initiated in accordance with Articles 31,36 or 37 of Council Directive 2001/83/EC-. Whatever the basis of the referral, the procedure used is always the procedure described in Articles 32,33 and 34 of Council Directive 2001/83/EC.

- For all non-centrally authorised medicinal products, regardless of the marketing authorisation procedure followed, safety concerns may be referred to the Agency for a CPMP Opinion under the provisions of Article 31 of Council Directive -2001/83/EC in specific cases where the interests of the Community are involved¹⁰, before reaching a decision on the suspension or withdrawal of an authorisation or on a variation to the terms of a marketing authorisation. Such referral can be initiated by Member States, the Commission or the MAH
- Notwithstanding the above, for medicinal products authorised under the Mutual Recognition Procedure or ex-Concertation products, the principal legal basis for a Member State referral is either Article -36 (i.e. for medicinal products authorised under the Mutual Recognition Procedure) or 37 - (i.e. for ex-Concertation medicinal products). Article -36 also applies to medicinal products which have already been subject to the procedure set out in Articles -32,33 and 34 of Council Directive -2001/83/EC
- A referral under Article 36- is appropriate where a Member State considers that a variation, suspension or withdrawal of a Marketing Authorisation for such medicinal products is considered necessary for the protection of public health.
- A referral under Article -36 is appropriate where a Member State has decided, in exceptional cases, where urgent action is essential to protect public health and until a definitive decision is adopted, to suspend the marketing and the use of the medicinal product concerned on its territory.

If considered necessary in order to protect public health, other medicinal products containing an active substance of the same therapeutic class may also be referred, where a class effect is the subject of this procedure.

- **Member States' notification of safety concerns**

In addition it should be noted that Article -107 of Council Directive -2001/83/EC places an obligation on the Member States to inform the Agency and the Marketing Authorisation Holder of the need of

¹⁰ "Community interest" refers to the interest of community public health related to a medicinal product which is on the market in the European Union, in the light of new data relating to quality, safety or efficacy or new pharmacovigilance information available and will require justification by the party making the referral.

any variation, suspension or withdrawal of a Marketing Authorisation for any medicinal product authorised as a result of the evaluation of adverse reaction reports. In the case that a Member State suspends the Marketing, the Agency has to be informed at the latest the following working day. The Agency secretariat will include the issue on the agenda of the following CPMP meeting for consideration¹¹.

2. The Procedure_____

2.1 Who makes the referral?

- The Commission and MAH(s) may refer to the CPMP safety concerns related to any Non-centrally authorised medicinal product only under Article 31
- Member States may make a referral to the CPMP for medicinal products authorised through purely national procedures in accordance with Article 31 only; whereas in the case of Mutual Recognition medicinal products, ex-Concertation medicinal products and medicinal products which have already been subject to the Articles 32, 33 and 34 procedure, the referral can only be based under Articles 36 and 37.

The party making the referral should clearly identify **the question** which is referred to the Committee for consideration, should justify Community interest, and where appropriate should identify all medicinal products concerned in the referral.

2.2 The question referred to the Committee

The question referred to the Committee should only be based on public health concerns and should be defined precisely.

At the first CPMP meeting following the referral, the Committee will formulate the question(s) to be addressed to the Marketing Authorisation Holder(s). The CPMP may also take into account other elements concerning quality, safety and efficacy of the medicinal product and which may aid in arriving at its Opinion.

2.3 Supporting elements

When an issue is referred under Article 31, 36 or 37 each Member State must make available to the Agency secretariat before the end of the first CPMP meeting following the referral a list of the names of the medicinal product(s), Marketing Authorisation Holder(s), pharmaceutical form(s) and strength(s) available in their territory.

The Member State or Marketing Authorisation Holder(s) should submit all available information relating to the matter in question to the Committee. In cases where the referral follows the suspension of the marketing of a medicinal product in a Member State, that Member State should immediately forward all information relating to this action to the CPMP members, the competent authorities of the Member States, and the Agency secretariat.

In the case of referrals from (a) Marketing Authorisation Holder(s), the referral must be accompanied by expert reports which take account of the current regulations and which have been updated to include data supporting the reasons for referral. In addition the Marketing Authorisation Holder(s) must ensure that all available information relating to the matter in question is forwarded to the CPMP members, the competent authorities of the Member States, and the Agency secretariat.

¹¹ The CPMP could just be informed of the action already taken by that Member State, and/or presented with the Member State decision to trigger a referral at that CPMP meeting or afterwards.

Referrals made by (a) Marketing Authorisation Holder(s), will incur payment to the Agency of a fee (30.000 ECU) which is due on the date of the referral.. Article 8(2) of Council Regulation (EC) No. 297/95 on fees payable to the Agency, as amended (Commission Regulation 494/2003 of 18 March 2003) would permit the Executive Director to refuse or suspend the procedure in case of non-payment.

2.4 Procedure and timetable

The Agency secretariat, on behalf of the Commission or the Member States, shall inform the Marketing Authorisation Holder(s) about the referral.

The referral is initiated by the letter sent by the party who makes the referral i.e. Commission, Member State or Marketing Authorisation Holder(s). The procedure will start on the first meeting day of the Committee following the referral. The legal provisions for this procedure, set out in Council Directive 2001/83/EC 31 -37 **Who may be appointed Rapporteur?**

The appointment of a Rapporteur and, if appropriate, a Co-Rapporteur for the procedure is made by the CPMP on a case-by-case basis. In cases where a number of referrals are made, related to a class effect, it is not necessary to appoint a (Co-)Rapporteur for each medicinal product. One (Co-) Rapporteur may be appointed for a class of products.

- **Timetable for the procedure.**

The Committee considers the matter and issues an Opinion within 90 days of the date of the start of the procedure. In case of an Article 31 referral, this period may be extended by 90 days. In cases of urgency, on a proposal from its Chairperson, the Committee may agree to impose a shorter deadline. Therefore the timetable and the deadline(s) for responses from the MAH(s) must be determined on a case by case basis depending on the urgency of the matter.

A general timetable for the procedure can be summarised as follows:

- Day 1:
- First meeting of the Committee following the referral to discuss the question(s) referred to the Committee and the appointment of the Rapporteur (Co-Rapporteur, where appropriate).
 - Question(s) to be addressed to the Marketing Authorisation Holder(s) adopted by the CPMP, based on the referral letter as well as any other aspect of which it has knowledge concerning the quality, safety and efficacy of the medicinal product and which may aid in arriving at its Opinion.
 - Adoption of a timetable for the responses to the questions. When determining the time allowed to the company to submit its responses the CPMP will bear in mind the urgency of the situation.
- clock stop
clock
re-start
- Agency secretariat informs the Marketing Authorisation Holder(s) of the (Co-) Rapporteur and Agency Product team leader and sends Question(s); clock stop for the company to answer the list of questions raised by the CPMP.
 - submission of responses; clock restart.
 - adoption by the CPMP of a timetable for the rest of the procedure.
- Day 40
- (Co-)Rapporteur(s) prepare(s) an assessment report on matter under referral, taking into account the written comments from the Marketing Authorisation Holder(s), together with proposals for revision of the SPC, if appropriate.
- Day 55
Day 60:
- Comments from CPMP Members on the (Co-)Rapporteur(s) assessment report(s).
 - Request for oral explanation, if necessary: (Co-)Rapporteur(s) and Agency secretariat to liaise with the Marketing Authorisation Holder(s).
 - Discussion at the CPMP.
 - Preparation of Draft CPMP assessment report by the Agency secretariat, incorporating the conclusions of the (Co-)Rapporteur(s).
- clock stop
- for the preparation of the oral explanation, if necessary.
- Day 90:
- Oral explanation if necessary.
 - Adoption of the CPMP Opinion with Annexes.

2.5 The Scientific Committee Opinion

The CPMP Opinion will be prepared by the Agency secretariat according to the appropriate template.

Although the Committee's primary concern is to reply to the question referred to it, there is nothing to prevent it to take into account any other element of which it has knowledge concerning the quality, safety and efficacy of the medicinal product and which may aid in arriving at its Opinion.

Where the Committee is of the opinion that the Marketing Authorisation should be maintained or varied, the following documents should be annexed to the Opinion:

- A complete SPC.
- Any conditions affecting the authorisation considered essential for the safe and effective use of the medicinal product
- Scientific conclusions on the basis of the Opinion of the CPMP

When this is not the case and the Committee is of the Opinion that the Marketing Authorisation should be suspended or withdrawn, the following document should be annexed to the Opinion:

- Scientific conclusions on the basis of the Opinion of the CPMP, including the grounds for suspension or withdrawal of the Marketing Authorisation.

In all cases, the CPMP Opinion should be accompanied by the CPMP assessment report.

2.6 Appeal and final Opinion.

The Opinion and its annexes will be sent to the Translation Centre in Luxembourg by the Agency secretariat, for translation into the official languages of the EU.

Once adopted by the CPMP, the Opinion and its annexes (in English) and the CPMP assessment report will be distributed by recorded delivery to the Marketing Authorisation Holder(s) by the Agency secretariat. The Marketing Authorisation Holder(s) will be given the opportunity to appeal.

The following timetable should be respected for any appeal by the Marketing Authorisation Holder(s):

Day 1: Receipt of Committee's Opinion.

Day 15: Marketing Authorisation Holder(s) should have notified the Agency of an intent to appeal.

Day 60: Marketing Authorisation Holder(s) should have notified the Agency of grounds for appeal.

Days are counted as calendar days, where the last day in a specified period falls on a Saturday, Sunday or public holiday the following working day will be considered as the final day.

At the first CPMP meeting following receipt of valid intent(s) to appeal the Opinion, the Committee will adopt a timetable for the appeal procedure. The Committee may choose to appoint a new (Co-) Rapporteur for the appeal.

Upon receipt of the grounds for appeal, the (Co-)Rapporteur(s) should prepare (an) assessment report(s) within 30 days. Comments from CPMP members should be made within the following 25 days. A revised CPMP assessment report taking into account the appeal will be drafted by the Agency secretariat. Within 60 days of receipt of the grounds for appeal, the Committee should reconsider its Opinion, and adopt a final CPMP Opinion.

The final Opinion and its annexes will be sent to the Translation Centre in Luxembourg by the Agency secretariat, for translation into the official languages of the European Union.

- **When does the Scientific Committee's Opinion become final?**

After the completion of the appeal procedure or if after 15 calendar days the Marketing Authorisation Holder(s) do(es) not appeal, the Opinion of the Committee becomes final.

This final Opinion accompanied by the annexes is then forwarded in the official EU languages, together with the CPMP assessment report (i.e. final updated assessment report to take account of the appeal) to the Member States, the Commission and, where there has been an appeal, to the Marketing Authorisation Holder(s).

3. Commission Decision and Its Implementation by Members States

Once the final CPMP Opinion is received at the Commission, the Decision making process starts in accordance with the procedure set out in Council Regulation (EEC) No. 2309/93 and Commission Regulation (EC) No. 1662/95, described in detail in chapter 6 of the revised *Notice to Applicants* (Volume 2A of *The Rules Governing Medicinal Products in the European Union*). <http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm>

The Decision will be addressed to all Member States concerned and the MAH(s). The Member States concerned will have to withdraw, suspend or vary the Marketing Authorisations as necessary to comply with the Decision, including the implementation of a revised SPC when appropriate. This Decision must be implemented within 30 days of notification of the Commission Decision.

Points other than those covered by the Decision can be subject of a new CPMP referral, based either on Article 29,30,31, 36 or 37 Council Directive 2001/83/EC or

**2.6 PRINCIPLES OF PROVIDING THE WORLD HEALTH ORGANIZATION WITH
PHARMACOVIGILANCE INFORMATION**

Background

As laid down in Article 25 of Council Regulation (EEC) No 2309/93, the Agency shall collaborate with the World Health Organization (WHO) on international pharmacovigilance and shall submit promptly to WHO appropriate and adequate information regarding the measures taken in the European Union related to the marketing authorisations of centrally authorised medicinal products which may have a bearing on public health protection in third countries.

Therefore, the CPMP Pharmacovigilance Working Party discussed and agreed during its meeting on 13-14 January 1998 the principles of how to provide the WHO Headquarters in Geneva and the WHO Collaborating Centre for International Drug Monitoring in Uppsala with such pharmacovigilance information¹².

In addition, the Pharmacovigilance Working Party also agreed on the principles for the provision of pharmacovigilance information for non-centrally authorised medicinal products.

1. Agreed Principles

• Adverse Drug Reaction Reports

Adverse drug reactions (ADRs) occurring in the EU will be reported to the WHO Collaborating Centre for International Drug Monitoring by the member state in whose territory the ADR has occurred. This applies to reports for centrally and non-centrally authorised medicinal products sent to the competent authorities either by health care professionals or by the marketing authorisation holders. ADRs occurring in Luxembourg will be transmitted to the WHO Centre by the French competent authority. ADRs occurring outside the EU will not be reported in order to avoid duplication at the WHO Centre and in particular to respect the information policies of third countries and their agreements with the WHO Centre.

• Rapid Alerts

Rapid alerts will be sent for non-centrally authorised medicinal products by the Member States and for centrally authorised products by the Agency in agreement with the European Commission if definitive measures related to the marketing authorisations of medicinal products (restriction, variation, suspension, withdrawal) are implemented by the competent authority or if the rapid alert informs about a public statement (positive or negative) made by the competent authority.

• Infofaxes

Infofaxes will not be sent as they deal with less urgent information usually at an early stage of investigation. This information is therefore in most cases pre-mature.

• Other Pharmacovigilance Information for Centrally Authorised Products

The Agency will inform about any regulatory action concerning centrally authorised medicinal products in case of safety reasons once the Commission Decision is granted. The Agency will also transmit any other public statements concerning centrally authorised medicinal products.

¹² ADR reports will only be sent to Uppsala.

- **Outcomes of Referrals**

The Agency will inform about the outcome of a referral procedure initiated in case of safety reasons once the Commission Decision is granted. The Agency will also transmit any other public statements concerning such products.

- **CPMP Position Statements on Pharmacovigilance Issues**

The Agency will transmit CPMP Position Statements on pharmacovigilance issues once they are released to the public.

In addition, Member States will provide further information for nationally authorised products according to their legislation and agreements.

3. Terminology

Introduction

This chapter is divided into two sections. Section 1 provides a glossary and includes the terms and definitions in common usage for pharmacovigilance purposes. Section 2 provides an overview of MedDRA, the Medical Dictionary for drug regulatory activities.

1. Glossary

Terms defined in the Community legislation are included in **boldface type**.

Additional interpretational guidance is included underneath in normal type.

Definitions used in the electronic reporting sections are included in *Italics*.

Abuse/Drug Abuse

Drug abuse is persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

Acknowledgement message

The acknowledgement message is the information provided to acknowledge one safety message and the safety report(s) contained in the safety file of this message, exchanged between one sender and one receiver in one transaction.

Adverse Reaction/ Adverse Drug Reaction (ADR)

Adverse reaction means a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Adverse drug reaction in this context is considered as synonymous with adverse reaction and suspected adverse drug reaction.

A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or a reviewing health-care professional. If a reaction is spontaneously reported by a health-care professional, this usually implies a positive judgement from the reporter unless the reporter explicitly gives a negative judgement on the causal relationship.

See also Adverse event, Serious adverse reaction Unexpected adverse reaction, Listed adverse drug reaction, Reportable Adverse reaction, Unlisted adverse drug reaction

Adverse Event (or adverse experience) (AE)

An undesirable experience occurring following administration of a medicinal product. An adverse event does not necessarily have a causal relationship with the treatment.

Case Safety Report

A case safety report is a document providing the most complete information related to an individual case available at a certain point of time.

Company Core Data Sheet (CCDS)

A document prepared by the marketing authorisation holder (MAH) containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)

All relevant safety information contained in the company core data sheet (CCDS) prepared by the marketing authorisation holder (MAH) and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (cut-off date)

The date designated as the cut-off date for data to be included in a periodic safety update report (PSUR).

Drug Abuse

See Abuse

EU Birth Date (EBD)

The date of the first marketing authorisation for a medicinal product granted in the European Union (EU) to the marketing authorisation holder:

- For medicinal products authorised through the centralised procedure, the EU Birth Date is the date of the marketing authorisation granted by the European Commission (Commission Decision date).
- For medicinal products authorised through the mutual recognition procedure, the EU Birth Date is the date of the marketing authorisation granted by the reference Member State.
- For products authorised nationally, the marketing authorisation holder may propose an EU Birth Date which can be applied to reporting requirements across the Member States.

See also International Birthdate

Health Care Professional

For the purposes of reporting suspected adverse reactions, health care professionals are defined as physicians, dentists, pharmacists, nurses and coroners. When reports originate from health-care professionals other than physicians and dentists, further information about the case should be obtained from a medically-qualified person if possible.

Individual Case

An individual case is the information provided to describe suspected adverse drug reaction(s) related to the administration of one or more medicinal products to an individual patient or to one or more animal(s).

International Birth Date (IBD)

The date of the first marketing authorisation for a medicinal product granted to the marketing authorisation holder (MAH) in any country in the world.

Listed Adverse Drug Reaction

An adverse reaction whose nature, severity, specificity and outcome are consistent with the information in the company core safety information (CCSI).

Minimum Information

See Reportable Adverse Reaction - Minimum Information

Periodic safety update reports (PSUR)

Periodic safety update reports means the periodical reports containing the records referred to in Article 104 of Council Directive 2001/83/EC

The reports referred to in Article 22.2 of Regulation 2309/93 are also known as periodic safety update reports.

Post-authorisation Study

A post-authorisation study is any study conducted within the conditions of the approved Summary of Product Characteristics (SPC) or under normal conditions of use. A post-authorisation study may sometimes also fall within the definition of a post-authorisation safety study (PASS). In relation to ADR reporting and PSUR requirements, reference to a post-authorisation study means any post-authorisation study of which the marketing authorisation holder is aware.

Post-authorisation Safety Study (PASS)

Post-authorisation safety study means a pharmacoepidemiological study, or a clinical trial carried out in accordance with the terms of marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

For the purpose of the guidance in chapter 1, section 1.5, any study where the number of patients to be included will add significantly to the existing safety data for the product, will also be considered a PASS. Chapter 1, section 1.5 of these chapter applies to company-sponsored PASS studies.

PSUR

See Periodic Safety Update Report

Receiver

The receiver is the intended recipient of the transmission.

Reportable Adverse Reaction - Minimum Information

A reportable adverse drug reaction (ADR) requires the following minimum information:

- (a) an identifiable health-care professional reporter -

The reporter can be identified by either name or initials, or address or qualification (e.g. physician, dentist, pharmacist, nurse).

- (b) an identifiable patient -

The patient can be identified by initials or patient number, or date of birth (or age information if date of birth not available) or sex. The information should be as complete as possible.

- (c) at least one suspected substance/medicinal product

- (d) at least one suspected adverse reaction.

The minimum information is the smallest amount of information required for the submission of a report and every effort should be made to obtain and submit further information when it becomes available.

When information is received directly from a patient (or a relative) suggesting that a serious adverse reaction may have occurred, the marketing authorisation holder should attempt to obtain relevant information from a health-care professional involved in the patient's care. On receipt of such information the case can be considered to be reportable. When a patient reports an adverse reaction and submits medical documentation, this should be considered sufficient to be reportable if it provides the minimum information and corroborates the patient's report.

Reporter

The reporter is the primary source of the information, i.e. a person who initially reports the facts. This should be distinguished from the sender of the message, though the reporter could also be a sender (ICH E2B).

The safety message is the information provided for one/more case safety reports contained in one safety file exchanged between one sender and one receiver in one transaction.

Safety Message File

The safety message file is the electronic file transmitted in one transaction between one sender and one receiver containing one safety message.

Sender

The sender is the person or entity creating the message for transmission. Although the reporter and the sender may be the same person, the function of the sender should not be confused with that of the reporter.

Serious Adverse Reaction

Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

It also includes serious adverse clinical consequences associated with use outside the terms of the Summary of Product Characteristics (SPC) (including, for example, prescribed doses higher than those recommended), overdoses or abuse.

Medical judgement should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient should be considered as serious.

Spontaneous Report or Spontaneous Notification

A communication to a company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study.

Transaction

A transaction is a set of actions encompassing the electronic transmission of a message.

Unexpected Adverse Reaction

Unexpected Adverse Reaction means an adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics.

It also includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product.

For products authorised nationally, the relevant SPC is that approved by the competent authority in the member state to whom the reaction is being reported.

For centrally authorised products, the relevant SPC is the SPC authorised by the European Commission. During the time period between a CPMP Opinion in favour of granting a marketing authorisation and the Commission Decision granting the marketing authorisation, the relevant SPC is the SPC annexed to the CPMP Opinion.

Unlisted Adverse Drug Reaction

An adverse reaction which is not specifically included as a suspected adverse effect in the company core safety information (CCSI). This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as occurring with this product.

2. MedDRA (Medical Dictionary for Regulatory Activities)

2.1 Introduction

MedDRA (Medical Dictionary for Regulatory Activities) was developed to standardise regulatory communication between the authorities responsible for the authorisation of medicinal products as well as the exchange between authorities and biopharmaceutical companies; data related to safety, quality or efficacy of medicinal products. Developed from the European Union system, MedDRA (Medical Dictionary for Drug Regulatory Affairs) under the auspices of the ICH (International Conference on Harmonisation), MedDRA has been developed as an internationally, clinically validated medical terminology for utilisation in data entry, retrieval, evaluation and presentation, in both pre-and post-marketing phases of regulatory processes. These processes include:

- Clinical studies
- Reports of spontaneous adverse reactions and events
- Regulatory submissions
- Regulated product information

Unlike many other terminologies, which typically need to be used in conjunction with yet another terminology, MedDRA allows its users to use one terminology for multiple purposes. The development and maintenance of MedDRA supports:

- Both pre- and post-marketing data
- Covering multiple medical product areas
- Availability in multiple formats
- Highest standards of maintenance
- A multilingual environment

There were terminology requirements within the industry, which led to the development of MedDRA.

- Use of different types of terminologies
- Use of terminologies for different phases of regulatory cycle
- Lack of specific terms
- Limited data retrieval options utilising current terminology
- Use of non-standard terminologies developed “in-house”
- High cost and time investment

2.2 MedDRA Scope

Terms found in MedDRA

- Diseases

- Diagnosis
- Signs
- Symptoms
- Therapeutic indications
- Investigation names and qualitative results
- Medical and surgical procedures
- Medical, social, family history
- Terms from: COSTART, WHO-ART, ICD-9 (some), ICD-9CM and HARTS

Terms NOT found in MedDRA

- Population level qualifiers (e.g. rare and frequent fail to focus on the individual patient)
- Numerical values for results (you can not universalise numeric representations, especially in terms of the measurement parameter)
- Severity descriptors (typically, terms such as severe or mild are not found in the terminology, some exception when their presence is medically relevant, e.g. aggravated conditions are different than the condition its self)
- Medical product terms (except a very small number pertaining to clinical lab tests)
- Patient demographics (aside from very few occasions where sex is a pertinent descriptor, terms like age, race and religion are not included in the terminology)
- Equipment, device and diagnostic product terms (e.g. the term catheter would not be include in the terminology where as the failure and its health effects would be)

2.3 MedDRA Structure

MedDRA is a five level multi-axial terminology. The relationship between terms fall into one of three categories:

Hierarchical - provides vertical links between superordinate (broad grouping) terms and subordinate (higher level of specificity) descriptors.

- System Organ Class (SOC)
- High Level Group Term (HLGT)
- High Level Term (HLT)
- Preferred Term (PT)
- Lowest Level Term (LLT)

Equivalence - grouping of synonymous terms. This is only exemplified in the relationship between the LLT and the PT.

Associative - allows terms to be linked horizontally, which are neither equivalent, nor hierarchically related but have a strong relation by sign, symptom, disease and diagnosis. This is only exemplified in the Special Search Categories.

The 26 System Organ Classes (SOC) in MedDRA represent parallel axes, which are not mutually exclusive. This allows terms to be represented in more than one SOC, and therefore grouped by different classifications. One single medical concept can be represented in more than one medical discipline. For example, the term Congenital HIV infection is represented in the following SOCs:

- Congenital and familial/genetic disorders
- Pregnancy, puerperium and perinatal conditions
- Infections and infestations
- Immune system disorders

2.4 Special Search Categories

Special Search Categories (SSC) allow linkage of terms which are neither equivalent nor hierarchically related but share clinical concepts that cross SOC hierarchies. This is accomplished by grouping terms at the PT level that are all relevant to the same, singular issue. This is usually a disease or syndrome.

2.5 MSSO (Maintenance and Support Services Organization)

The ICH Steering Committee recognised that a vital factor and distinguishing characteristic of MedDRA must be the long-term maintenance and updating of the terminology and its evolution in response to medical/scientific advances and changes in the regulatory environment. Through an open, competitive tender the MSSO (Maintenance and Support Services Organisation) was established. The 5-year contract naming TRW as the prime contractor for the MSSO was signed in November 1998.

Two objectives were defined for the MSSO:

- Establish a mechanism for international support, development and distribution of the MedDRA terminology.
- Foster the use of MedDRA world-wide through communication, education, products and services.

The MSSO is charged to house, maintain and distribute MedDRA. MedDRA was initially be maintained in English and, through the Japanese Maintenance Organization (JMO), Japanese. Translations in French, German and Spanish are provided by the appropriate European regulatory authorities.

2.6 Contact the MedDRA MSSO

For MedDRA subscription information, contact the MSSO:

MedDRA MSSO	Toll-Free Worldwide: 877.258.8280 (AT&T)
c/o TRW	Direct: 00 1 703.345.7799 (USA)
VAR1/6A/MSSO	Fax: 00 1 703.345.7755

12011 Sunset Hills Road

E-Mail: subscrib@meddramsso.com

Reston, VA 20190-3285

Web Site: www.meddramsso.com

USA

2.7 Use of MedDRA in the EU

The use of MedDRA in the EU is mandatory for all regulatory adverse drug reaction reporting from January 2003. . The practical methodologies for use of MedDRA in the EU, taking into account the different language versions are developed by a MedDRA implementation group and will be incorporated into this guide on completion.

PART II - VETERINARY MEDICINAL PRODUCTS

Section 1: Guidance and Procedures for Marketing Authorisation Holders

1. Legal Basis and Purpose

The legal framework for pharmacovigilance of veterinary medicinal products in the Community is given in Council Regulation (EEC) No 2309/93 (Title III, Chapter 3), Commission Regulation (EC) No 540/95 and Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

Pharmacovigilance activities come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the veterinary medicinal product used under field conditions.

Pharmacovigilance obligations apply to all authorised veterinary medicinal products.

Council Regulation No 2309/93 (Articles 41 to 44), Commission Regulation (EC) No 540/95 and Directive 2001/82/EC (Title VII articles 72 to art.78) describe the respective obligations of the person responsible for placing the veterinary medicinal product on the market (the Marketing Authorisation Holder) and of the competent authorities, to set up a system for pharmacovigilance in order to collect, evaluate and collate information about suspected adverse reactions. All relevant information should be shared between the competent authorities and the Marketing Authorisation Holder (MAH), in order to allow the partners in pharmacovigilance activities to assume their obligations and responsibilities. This requires an exchange of information between the Agency, the competent authorities of the Member States, the Commission and the Marketing Authorisation Holder, as well as procedures to avoid duplications, maintain confidentiality and ensure the quality of the systems.

These guidelines introduce some new concepts for veterinary medicinal products such as post authorisation surveillance studies and reinforce others, such as risk/benefit evaluation. Specific methodological technology and procedures will need to be developed in the near future and these will involve the European Commission, the Agency, the competent authorities from Member States as well as interested parties..

As indicated in the foreword, this guidance for Marketing Authorisation Holders on the implementation and practical procedures involved in complying with the above legislation, in the interests of protecting public and animal health, has been prepared in accordance with Article 46 of the Council Regulation No2309/93 and Article 77.1of the Directive 2001/82/EC.

2. Pharmacovigilance reporting

The scope of veterinary pharmacovigilance as defined in Article 73 of Directive 2001/82/EC covers not only suspected adverse reactions in animals to veterinary medicinal products used under normal conditions of use, but also other aspects of post-authorisation surveillance. The system also takes into account any available information related to:

- Adverse reactions in humans related to the use of veterinary medicinal products;
- Lack of expected efficacy of veterinary medicinal product;
- Off-label use of veterinary medicinal product
- Reported violations of approved residue limits, possibly leading to investigations of the validity of the withdrawal period .
- Potential environmental problems

For all veterinary medicinal products authorised in the Community (whether through the Community or national procedures):

all Suspected Adverse Reactions (serious or otherwise) should be reported when received from veterinarians, other animal health professionals, animal owners or users of the veterinary medicinal product. For the accuracy and usefulness of the information reported, it is recommended for animal owners and other users to seek veterinary advice prior to reporting. Suspected Adverse Reactions (SAR) should be reported even if the Marketing Authorisation Holder (MAH) does not agree with the reporter's assessment of a possible causal association. These include spontaneously reported suspected adverse reactions and suspected adverse reactions from post-authorisation surveillance studies.

2.1 Reporting of human adverse reactions to veterinary medicinal products

All suspected adverse reactions occurring in humans following use of veterinary medicinal products should be reported immediately by the MAH, and in no case later than 15 calendar days following receipt, to the competent authorities of the member state in whose territory the incident occurred. (See section 7 for details of what to report).

2.2 Reporting of lack of expected efficacy

Directive 2001/82/EC cites the lack of expected efficacy as a reason for refusal or revocation of authorisation. It is incumbent therefore for MAH to investigate such reports.

Where the conclusions drawn from the suspected adverse reaction reports differ from those in the dossier on which the authorisation was granted and which might normally be expected on efficacy, the MAH should inform the competent authority.

Lack of expected efficacy in this context means: lack of efficacy of a veterinary medicinal product according to the indications authorised in the marketing authorisation..

2.3 Off-label use¹³

Reports of suspected adverse reactions may be obtained on veterinary medicinal products used outside the terms of the marketing authorisation e.g. use in non-authorised species/indications, use at doses differing from those set out in the relevant summary of product characteristics (SPC).

While this practice is neither endorsed nor recommended, such reports can provide useful information on the safety of the veterinary medicinal product and should be recorded by the person responsible for pharmacovigilance and reported to the competent authorities.

2.4 Pre-mixes for medicated feedingstuffs¹⁴

When pre-mixes which have been incorporated in the finished medicated feed are suspected of causing an adverse reaction in animals or humans, both the premix and the medicated feed should be investigated and the report sent without delay. Among the factors that have to be examined are the composition of the finished medicated feed, the inclusion levels of active substances, the operation of the milling process(es) and, when possible, the actual dosage administered to individual target animals.

¹³ Off-label use: the use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product.[as defined in Article 1(16) of Dir.2001/82/EC]

¹⁴ Pre-mix for medicated feedingstuffs; any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.[as defined in Article 1(5) of Directive 2001/82/EC]

2.5 Investigation of the validity of the withdrawal period [reporting of violations of approved Maximum Residue Limits (MRLs)]

Where investigation of residues of veterinary medicinal products in tissues or products from treated animals casts doubt on the validity of the withdrawal period in respect of the veterinary medicinal product used, it is important that this information is brought to the attention of the competent authority responsible for authorisation of the veterinary medicinal product concerned. Such cases should be reported as suspected adverse reactions in the Periodic Safety Update Reports (see 6.3.7iii).

2.6 Use of human medicinal products in animals

Occasionally suspected adverse reaction reports may be obtained from human medicinal products having been used in animals, where legislative circumstances allow. Such reports can provide useful information on the safety or otherwise of the medicinal product ingredients and should be reported by the veterinarian who used the human medicinal product and, if appropriate, the veterinary representative of the Marketing Authorisation Holder of the human medicinal product concerned.

3 Responsibilities of Marketing Authorisation Holder

The responsibilities of the qualified person responsible for pharmacovigilance are as follows:

- 3.1** the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the MAH, including representatives, is collected and collated so that it may be accessible at least at one point within the Community, as indicated by the MAH;
- 3.2** the preparation and submission of the following documents for the Agency and/or competent authorities of Member States where the veterinary medicinal product is authorised as referred to in the Regulation N°2309/93 and Directive 2001/82/EC and further detailed in this document:
 - Serious Suspected Adverse Reaction reports
 - Periodic Safety Update Reports to include:
 - ongoing risk/benefit evaluation during the post-authorisation period;
 - all (serious and non-serious) spontaneous adverse reaction reports involving animals or humans, including reports of lack of expected efficacy or off-label use of the veterinary medicinal product;
 - potential environmental problems;
 - investigations of the validity of the withdrawal period due to reported violations of approved Maximum Residue Limits;
 - Reports of suspected adverse reactions in humans
- 3.3** Ensuring that any request from the competent authorities in any Member States, for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a veterinary medicinal product, is answered fully and promptly. This includes the provision of information about the volume of sales of the veterinary medicinal product concerned;
- 3.4** Ensuring that suspected adverse reactions to veterinary medicinal products authorised under Article 13.(1)(a)(i) Directive 2001/82/EC are reported to the competent authorities. The MAHs

for both the original reference product (Product A) and the essentially similar product (Product B, authorised according to Article 13.(1)(a)(i) of Directive 2001/82/EC) assume full responsibility for the pharmacovigilance relating to their respective products.

Nevertheless they should maintain close liaison, and in particular suspected adverse reactions to Product B must be communicated to the Marketing Authorisation Holder for Product A. Where identical products are co-marketed by more than one company any report of a serious suspected adverse reaction must be communicated by one company to another. Any regulatory action resulting from pharmacovigilance information related to the veterinary medicinal products involved in the above scenarios would need to be applied as appropriate to both veterinary medicinal products.

- 3.5** If the MAH is aware that a original reporter has reported a adverse reaction to one of its veterinary medicinal products directly to the competent authority of a Member State, the MAH should still report the adverse reaction, informing the competent authority that the report is likely to be a duplicate of a previous report. In this situation it is essential for the Marketing Authorisation Holder to provide all the available details, including any reference number provided to the original reporter by the competent authority, in order to aid identification of the duplicate.

4. Suspected Adverse Reaction Reporting

Adverse Reaction¹⁵: A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.[as defined in article 1.(10) of Directive 2001/82/EC]

- 4.1** The Marketing Authorisation Holder is responsible for reporting suspected adverse reactions to the competent authorities of the Member States and to the Agency for their veterinary medicinal products authorised under the centralised procedures and to the appropriate competent authorities of the Member States for their veterinary medicinal products authorised through the national procedures. (For details of the reporting requirements see sections 5.7)

- 4.2** Minimum requirements for any suspected adverse reaction (serious/non-serious/in human) report to be recorded by the Marketing Authorisation Holder, and reported to the competent authorities of Member State (and to the Agency for Community authorisations):

A case report will be considered as a suspected adverse reaction report provided that at least the following data are available:

- (i) An identifiable source, wherever possible this should include the name and address of the original reporter (e.g. veterinarian, pharmacist, animal owner)
- (ii) Animal details: species, sex, age / human details: sex, age or adult/child
- (iii) Suspect medicinal product - (Brand name and marketing authorisation number)
- (iv) Adverse reaction details

The reference point for deadlines for submission of reports is the time of receipt of the minimum information. It should be stressed that these are minimum requirements and that MAH should endeavour to provide all the information necessary for a full evaluation. (See sections 5.3 and 6.3 for details of information required).

¹⁵ Also referred to Suspected Adverse Reaction (SAR)

4.3 Suspected adverse reaction reports can be divided into the following:

- Serious Suspected Adverse Reaction Reports (see section 5)
- Periodic Safety Update Reports (see section 6)
- Human Suspected Adverse Reaction Reports (see section 7)

4.4 Reports from post-authorisation surveillance studies

During the post-authorisation period the veterinary medicinal product will be used in a different setting from clinical trials and larger animal populations are likely to be exposed. Much new information will be generated which may impact on the risk/benefit ratio and an evaluation of this needs to be an on-going process, both within Marketing Authorisation Holders and regulatory authorities.

Compared to human medicine, the tolerance of veterinary medicinal products is more predictable since it is studied in the target animal species at overdoses, which allows for the evaluation of a margin of safety. Therefore the need for post- authorisation surveillance studies is certainly not so stringent in the veterinary field. Spontaneous reporting schemes are expected to provide the complementary information concerning adverse reactions, especially those, which are unexpected. However, for specific cases concerning suspected adverse reactions occurring for veterinary medicinal products used on a large scale such as post-vaccinal reactions, post authorisation surveillance studies should be encouraged.

The methodology for such studies is obviously quite specific to the veterinary field and should be considered as an area for investigation in veterinary pharmacovigilance, and will be the subject of further guidelines. Serious suspected adverse reactions for post-authorisation studies should be reported to all Member States where the veterinary medicinal product is authorised. (See section 1.5 for reporting requirements.) Non--serious adverse reactions should be reported in summary at the end of each study and included in the Periodic Safety Update Report (see section 6).

5. **Serious Suspected Adverse Reaction Reporting**

Serious Adverse Reaction: An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect or which results in permanent or prolonged signs in the animals treated. [as defined in article 1.(12) of Directive 2001/82/EC]

In veterinary medicine, the existence of a diversity of animal species and husbandry conditions require a modified approach to the classification of a 'Serious Adverse Reaction'. For example in intensive animal production with species such as poultry, fish or bees, a certain level of mortality rate is considered usually as "normally probable". These species are usually treated as a group and only an increased incidence of mortality rate , or severe clinical symptoms, or exceeding variations of expected animal production rates could be considered as a 'serious' adverse reaction ..

However, in companion animal species like dogs or cats, a single death constitutes a serious adverse reaction. This also applies to cases of individual deaths in cattle, sheep, pigs, goats even if they are kept in herds or flocks in intensive animal production because treatment is often performed on the individual animal and therefore a single death or severe clinical symptoms have to be considered on an individual basis.

5.1 **Adverse Reaction reports occurring in the EEA**

Council Regulation (EEC) 2309/93 Article 44

Directive 2001/82/EC Article 75

Decision of the EEA Joint Committee No 74/1999 (OJ L284, 9.11.200, p.65)

The Marketing Authorisation Holder should record and report all suspected serious adverse reactions occurring within the EEA which are brought to its attention. These should be reported immediately, and in no case later than 15 calendar days from receipt, to the Member or EFTA State in whose territory the incident occurred. (See section 5.3 for details of what information is required).

For centrally authorised veterinary medicinal products, the responsibility for ensuring that all serious suspected adverse reactions occurring within their territory are further reported to the Agency, rests with the Member or EFTA States concerned. Such reports must be submitted to the Agency immediately, and in no case later than 15 days following receipt of the information

In addition, serious adverse reactions together with all other adverse reactions should be reported as line listings in the Periodic Safety Update Report (PSUR) (see section 6).

A general overview on the reporting of suspected adverse reactions in relation to the type of authorisation is presented in the Event Charts in Annex I.

5.2 Adverse Reaction reports occurring outside the EEA

Council Regulation (EEC) 2309/93 Article 44.

Directive 2001/82/EC Article 75

The Marketing Authorisation Holder should report all suspected serious and unexpected¹⁶ adverse reactions related to its veterinary medicinal product ,occurring in the territory of a third country and brought to its attention. These should be reported immediately to the Agency and to all Member States and in no case later than 15 calendar days following receipt.In addition, all unexpected adverse reactions from third countries should be reported as line listings in the PSUR (see section 1.6).

A general overview on the reporting of suspected adverse reactions in relation to the type of authorisation is presented in the Event Charts in Annex I.

5.3 Content/Required information for serious suspected adverse reactions (Single) reports

Marketing Authorisation Holders are expected to fully validate and follow-up all serious suspected adverse reactions reported by them to the competent authorities. It is essential for MAHs to provide as complete as possible details, including all relevant clinical information for each cases of serious suspected adverse reactions in order to facilitate causality assessment. The report of a suspected adverse reaction should as far as possible include the information below. The original words used by the reporter should be provided even if they are also classified or coded according to Marketing Authorisation Holder or competent authority accepted terminology.

5.3.1 Marketing Authorisation Holder details and original reporter's details

- i) The name of the qualified person responsible for pharmacovigilance employed by the MAH
- ii) Address, telephone and fax number of the qualified person responsible for pharmacovigilance.

¹⁶ Unexpected Adverse Reaction: This means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of the product characteristics .[as defined in article 13 of Directive 2001/82/EC]

- iii) MAH case reference number.
- iv) Date of receipt of report by MAH (in Member State where qualified person responsible for pharmacovigilance is established).
- v) Source of report (e.g. spontaneous, clinical trial, post-authorisation study.)
- vi) Details of the original reporter; name (if acceptable under national law), address, qualification/occupation (if appropriate).
- vii) Reporting country (country where the incident occurred).
- viii) Purchase country (where suspect veterinary medicinal product was purchased if different from that above).

5.3.2 Animal Details

- i) Number of animal(s) treated
- ii) Characteristics of animal(s) presenting signs:
 - Species
 - Breed
 - Sex
 - Age (in days/weeks/months/years)
 - Weight (in kilograms)

5.3.3 Suspect veterinary medicinal product details

- i) Veterinary Medicinal Product name(s)/brand names(s)
- ii) Approved Scientific Name(s) (INN - International Non-proprietary Name)
- iii) Marketing Authorisation Number
- iv) ATC vet Code (Therapeutic Group)
- v) Pharmaceutical form
- vi) Batch number
- vii) Expiry date of batch - if relevant
- viii) Storage details - if relevant

5.3.4 Treatment details

- i) The person who administered the veterinary medicinal product (e.g. animal owner, veterinarian etc.) Include identifier (name/initials) and relevant occupation/qualification of person
- ii) Reason for treatment including diagnosis

- iii) Dose (and frequency if relevant) of treatment given
- iv) Route and site of administration used
- v) Start date
- vi) Stop date and/or duration of treatment
- vii) Time between administration and adverse reaction to the veterinary medicinal product
- viii) Action taken after adversereaction (e.g. product withdrawn, dose reduced)
- ix) Previous adverse reaction(s) to the veterinary medicinal product if occurred/reported, (re-challenge information) to include:
 - Approximate date animal(s) previously treated with medicinal product
 - Description of adverse reaction including - were previous adverse reaction signs similar to the present adverse reaction signs
 - Outcome including any treatment given

5.3.5 Other products used concurrently

All medication used or administrated to, over at least a one week period preceding the suspected adverse reaction should be provided when available. This should also particularly include non-prescription veterinary medicinal products, magistral preparations¹⁷, officinal preparations,, medicated feedstuffs and additives in feedingstuffs if appropriate.

For each medication:

- i) Product name(s)/brand names(s)
- ii) Approved Scientific Name(s) (INN - International Non-proprietary Name)
- iii) Marketing Authorisation Number
- iv) ATCvet Code (Therapeutic Group)
- v) Pharmaceutical form
- vi) Batch number if relevant
- vii) Expiry date of batch if relevant
- viii) Storage details - if relevant

Treatment details for other product(s) used concurrently

- ix) The person who administered the product (e.g. animal owner, veterinary surgeon etc.) Include identifier (name/initials) and relevant occupation/qualification of person

¹⁷ In the case of magistral formulae products, details of individual constituents of the formulae should be indicated

- x) Dose (and frequency if relevant) of treatment given
- xi) Route and site of administration used
- xii) Start date
- xiii) Stop date and/or duration of treatment
- xiv) Other relevant information

5.3.6 Details of the animal suspected adverse reaction(s)

- i) Description of adverse reactions(s) including site and severity (intensity of the reaction). The original reporters words and/or phrases to be used where possible (with explanations if appropriate)
- ii) Start date or onset of reaction
- iii) Stop date or duration of reaction
- iv) Specific treatments adopted against the observed adverse reaction
- v) Number of animals showing signs
- vi) Number of animals dead
- vii) De-challenge information (e.g. any obvious effect of removal of treatment)
- viii) If available the following information should be provided:
 - Number of treated animals alive with sequelae
 - Number of treated animals recovered

Any previous adverse reactions to the product should be recorded under 5.3.4ix)

5.3.7 Other information

Any other relevant information available to facilitate assessment of the case should be provided, for example: disposition to allergy or changes in feeding habits, and/or production levels.

5.3.8 Investigation

- In a case of fatal outcome the cause of death should be investigated and its relationship to the suspected adverse reaction commented upon. Post-mortem examination findings or laboratory findings, if carried out, should be provided.
- Summary of investigation(s) on the sample of the suspected veterinary medicinal product (if relevant)
- Nature of MAH investigation (if relevant)

5.3.9 Causality assessment

Marketing Authorisation Holders may comment on whether they consider there is a causal association between the suspect veterinary medicinal product(s) and adverse reactions(s) reported and should provide the criteria on which they have made the causality assessment.

The causality assessment should be done using the ABONsystem if possible. According to this coding system, four categories of causality can be made:

- category "A" : probable
- category "B" : possible
- category "O" : unclassified (cases where insufficient information was available to draw any conclusion)
- category "N" : unlikely to be related to the veterinary medicinal product

In assessing causality the following factors should be taken into account:

- i) associative connection, in time - including dechallenge and rechallenge following repeated administration (in clinical history) - or in anatomic sites;
- ii) pharmacological explanation, blood levels, previous knowledge of the drug;
- iii) presence of characteristic clinical or pathological phenomena;
- iv) exclusion of other causes;
- v) completeness and reliability of the data in the case reports;
- vi) quantitative measurement of the degree of contribution of a product to the development of a adverse reaction (dose-effect relationship).

For inclusion in category "A" (probable), it is recommended that **all** the following minimum criteria should be complied with:

- There should be a reasonable association in time between the administration of the veterinary medicinal product and onset and duration of the reported adverse reaction..
- The description of the clinical event should be consistent with, or at least plausible, given the known pharmacology and toxicology of the veterinary medicinal product.
- There should be no other equally plausible explanation(s) of the case reported. (If such are suggested - are they validated? What is their degree of certainty?) In particular, concurrent use of other products , possible interactions, or intercurrent disease should be taken into account in the causality assessment.

Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information) then such reports can only be classified as "B" (possible), "N" (unlikely) or "O" (unclassifiable/unassessable).

For inclusion in category "B" (possible), it is recommended that this category code would be applied when the veterinary medicinal product is one of other possible and plausible causes for the reported event but where the available data does not meet the criteria for inclusion in category "A".

For inclusion in category "N" (unlikely), it is recommended that this category code would be applied to cases where sufficient information exists to establish beyond reasonable doubt that the veterinary medicinal product was not likely to be the cause of the adverse reaction..

For inclusion in category "O" (unclassifiable/unassessable), it is recommended that this category code would be applied to all cases where reliable data concerning a SAR is unavailable or is insufficient to make an assessment of causality.

5.3.10 Reporting form for MAHs

In accordance with Art.77(1) of Directive 2001/82/EC and Art.46 of Regulation No 2309/93 the European Commission, in consultation with the Agency, Member States and the interested parties has drawn up guidance on the collection, verification and presentation of suspect adverse reaction reports.

A standardised European Veterinary Pharmacovigilance Reporting Form for MAHs to report to Competent Authorities has been developed (EMEA/CVMP/601/02-final). This reporting form is provided in Table A and could also be downloaded at the following web address; <http://www.emea.eu.int/pdfs/vet/phvwp/EMEA-CVMP-601-02-Reportform-Final.doc>

The CVMP have also developed and adopted a list of standardised clinical terms, called “VEDDRA list of clinical terms “ to be used to describe the clinical signs of the adverse reaction occurring in animals after administration of a veterinary medicinal product.(EMEA/CVMP/413/99-final). This list is provided in PART III Annex I (English only until now) and could be downloaded at the following web address; <http://www.emea.eu.int/pdfs/vet/phvwp/veddra.csv>) or directly at the VEDDRA Web site (<http://www.veddra.org>).

6. Periodic Safety Update Reports (PSURs)

A Periodic Safety Update Report is intended to provide competent authorities with an update of the world-wide safety experience of a veterinary medicinal product at defined times period of post-authorisation. At these times Marketing Authorisation Holders (MAHs) are expected to provide succinct summary information together with a critical evaluation of the risk/benefit of the veterinary medicinal product in the light of any new or changing post-authorisation information. This is in order to ascertain whether further investigations need to be carried out and/or whether changes should be made to the SPC, labelling or product promotion.

6.1 Where to send Periodic Safety Update Reports

Periodic Safety Update Reports for veterinary medicinal products authorised under the centralised procedure should be submitted to all the competent authorities of Member States and to the Agency in accordance with Article 44 of Council Regulation (EEC) No 2309/93.

In accordance with Article 75 (4) of Directive 2001/82/EC, PSURs for veterinary medicinal products that fall within the scope of Directive 87/22/EC (Ex-concertation procedure) or which have benefited from the procedures under Articles 21, 22 and 32(4) of Directive 2001/82/EC or referrals under Articles 36, 37 and 38 of Directive 2001/82/EC, should be submitted to the competent authorities of Member States, in agreement with the reference Member State. .

6.2 Scope and frequency of PSURs

Unless other requirements have been laid down as condition of the granting of authorisation, a periodic safety update report , in the specified format (see Table B), should be prepared for all authorised veterinary medicinal products at the following intervals:

- immediately upon request
- 6-monthly for the first 2 years after authorisation
- annually for the subsequent 2 years
- at the time of the first renewal
- thereafter 5-yearly at the time of further renewal.

The requirement for submission of a PSUR applies irrespective of whether the veterinary medicinal product is marketed or not.

Each PSUR should cover the period of time since the last update report and should be submitted within 60 days after the Data Lock Point (DLP)¹⁸

Data lock points may be set according to the EU Birth Date (date of the first marketing authorisation within the European Union) of a veterinary medicinal product or its International Birth Date.

Preparation of PSURs according to the International Birth Date

¹⁸ Data Lock Point (DLP): The date designated as the cut-off date for data to be incorporated into a particular safety update. On this date the data available to the author of the safety report is extracted for review and stored.

Veterinary medicinal products, which are also authorised outside the EU, will have an International Birth Date (IBD). This is the date of the first marketing authorisation for the veterinary medicinal product granted to the Marketing Authorisation Holder in any country in the world. For veterinary medicinal products first authorised in the EU, the EU Birth Date is the IBD. For administrative convenience, if desired by the Marketing Authorisation Holder, the IBD may be designated as the last day of the same month.

In order to harmonise periodic safety updates internationally, the Marketing Authorisation Holder, may use the IBD to determine the data-lock points in the EU rather than the EU Birth Date. If the IBD is used, the first data lock point must be within 6 months of the EU Marketing Authorisation Date, unless other requirements have been laid down at the time of granting the authorisation.

Regardless of whether the IBD or EU Birth Date is used, the PSUR must always be submitted within the 60 days following the data lock point.

The Marketing Authorisation Holder should submit the renewal application at least three months before the expiry date of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate co-ordination with the regular cycle of the PSUR. At the time of the renewal application the Marketing Authorisation Holder should submit a PSUR no more than 60 days after the data lock point which should cover the intervening time period since the last PSUR.

For the purpose of the PSUR the Marketing Authorisation Holder's database should be frozen in relation to the veterinary medicinal product at the DLPs. Up-to-date safety data, i.e. data that becomes known to the Marketing Authorisation Holder after the DLP and which may influence the evaluation should also be included in the report in the final section (see 6.3.10). For veterinary medicinal products authorised under the centralised procedure in accordance with Council Regulation (EEC) No 2309/93, the PSUR should cover all authorised presentations covering all pharmaceutical forms and target species, whether authorised with the original marketing authorisation or at a later time point, e.g. through a variation of the original marketing authorisation. For each subsequent authorisation it will be decided on a case-by-case basis whether the submission cycle for the PSUR needs to be changed. The data lock points remain based on the original marketing authorisation.

In compliance with the requirements laid down in Commission Regulation (EC) No 540/95, MAHs must include in the periodic safety update reports details of all suspected unexpected adverse reactions, which are not classified serious, arising in the Community or in a third country.

6.3 Content of Periodic Safety Update Reports

A PSUR for a Community authorised product should be written in English. For nationally authorised products the PSUR should be written in the national language(s), or in English if this is acceptable to the appropriate competent authorities. All PSURs should fulfil the following format and content:

6.3.1 Summary of Product Characteristics (SPC) (Articles 12 and 14 Directive 2001/82/EC)

The latest authorised version of the relevant SPC (veterinary medicinal product authorised through the centralised or mutual recognition or national procedure) must be included for reference in the report.. If no SPC is available, e.g. in cases of old non-reviewed products, an explanation should be given and the package insert should be provided.

6.3.2 Update of regulatory or Marketing Authorisation Holder actions taken for safety reasons

An update should be presented if any significant regulatory-initiated or MAH- initiated actions have been taken, or are to be taken, for safety reasons during the reporting period anywhere in the world.

The format should be a brief narrative stating the reasons for significant regulatory or MAH action, with documentation appended when appropriate.

6.3.3 Sales volume

A safety update must address the relationship of sales volume of a veterinary medicinal product related to numbers of suspected adverse reactions reported.

For nationally authorised veterinary medicinal products, each PSUR should contain the number of doses/amount of veterinary medicinal product sold in the relevant Member States. For Community authorised veterinary medicinal products, each PSUR should contain the number of doses/amount sold in each Member State where the veterinary medicinal product is authorised. This should be expressed in an appropriate form.

The following forms are suggested:

- Vaccines to be expressed in numbers of doses;
- Liquid to be expressed in litres;
- Powder to be expressed in kilograms;
- Tablets to be expressed in numbers of tablets;
- Sprays to be expressed in litres or kilograms;
- Flea collars to be expressed in numbers of collars;
- Paste to be expressed in kilograms

The incidence of adverse reactions (%), should be calculated by dividing the total number of animals reacting during the period by the number of doses sold (in appropriate units) during the period of the report and multiplying by 100.

$$\text{Adverse reaction Incidence (\%)} = \frac{\text{Number of animals reacting during period}}{\text{No of doses sold during period}} \times 100$$

For both nationally and Community authorised veterinary medicinal product, adverse reaction incidence should be calculated individually for each country.

Where a veterinary medicinal product is authorised for more than one target animal species, and if reliable data are available, incidence of adverse reactions may be calculated and reported for each authorised target animal species. A number of PSURs will show no report of suspected adverse reactions. In these cases it will not be possible to calculate an incidence rate of adverse reactions.

6.3.4 Marketing Authorisation Holder and veterinary medicinal product details

Each PSUR should include:

- i) Name of the MAH
- ii) Veterinary medicinal product name(s)

- iii) Marketing authorisation number

6.3.5 Individual case histories

The minimum information constituting a reportable individual case is listed at 4.2

The standard information required for an individual case (line listing) includes:

- i) MAH case reference number (+ country where incident reaction/occurred if different to the country of the Member States concerned, or if Community authorised product)
- ii) Date(s) of treatment(s)/Date(s) of vaccination(s)
- iii) Was the product used as recommended?
- vi) Date of adverse reaction
- v) Number of animals treated
- vi) Species
- vii) Age(s)
- viii) Number of animal(s) reacted (approximate)
- ix) Number of animal(s) dead
- x) Other products used concurrently
- xi) Clinical signs/diagnosis
- xii) MAH comments and causality assessment (A, B, O, N code)

6.3.6 Reporting forms

All the individual case reports listed above should be presented in the line-listing format given in Table B.

6.3.7 Suspected adverse reaction reports to be included in the PSUR

The appropriate individual suspected adverse reaction reports defined below should be included only if received during the period of review.

- i) All spontaneous suspected adverse reactions reports (serious and non-serious)

All individual case reports sent spontaneously to the MAH as well as suspected unexpected adverse reactions classified as non-serious as required under Commission Regulation (EC) No 540/95

The line listing should also include all serious suspected adverse reactions that qualified for reporting by MAHs as full 15 day reports under the guidelines on adverse reaction reporting by MAHs. These cases should be identified (e.g. asterisked) in the comments section of the line listing (where MAHs have received reports from the competent authorities these should also be included in the line listing and identified in the comments section accordingly).

- ii) All serious suspected adverse reactions reports from other sources

MAHs sometimes receive adverse reaction information on individual cases from other sources. Those from competent authorities should also be listed, identifying their source (Competent authority case number, if available).

iii) Other reports to be included

Suspected adverse reactions reports related to the veterinary medicinal product used, as information on violations of approved Maximum Residue Limits, lack of expected efficacy, off-label use or any environmental problems, should be provided as fully as possible.

iv) Reports from post-authorisation studies

Serious and non-serious suspected adverse reaction reports from post-authorisation studies should be included as line listings in the PSUR (see section 4.4).

v) Narrative review of the individual case histories

The report should include a brief narrative based on the Marketing Authorisation Holder's analysis of the cases reported in the line listing. This should include any comment on variation in frequency and a causality assessment

6.3.8 Published adverse reaction reports

A brief narrative overview with a bibliography of published adverse reaction reports should be attached to the PSUR, if relevant.

6.3.9 Overall safety evaluation

The safety update should include a concise critical analysis and opinion on the risk/benefit profile of the veterinary medicinal product written by a suitably qualified expert for pharmacovigilance. Any new important information on the following should be explicitly included:

- i) evidence of previously unidentified toxicity
- ii) increased frequency of known toxicity
- iii) product interactions
- iv) overdose and its treatment
- v) suspected adverse reactions associated with off-label use
- vi) human adverse reactions associated with the use of the veterinary medicinal product.

For each of these points, lack of significant information should be reported.

The evaluation should indicate in particular whether the safety data remain in line with the cumulative experience to date and the authorised SPC, and should specify and justify any recommended action.

In the event of any new or changing information becoming available which impacts on, or may influence the overall benefit/risk evaluation of a veterinary medicinal product, the MAH should immediately inform all the competent authorities in countries in which the veterinary medicinal product is authorised; for Community authorised veterinary medicinal authorisation, the Agency should additionally be informed. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted at the earliest opportunity and no later than 4 weeks of being requested, to all competent authorities of the Member States in which the veterinary medicinal

product has been authorised and in addition, for veterinary medicinal products centrally authorised, the Commission and the Agency.

6.3.10 Important information received after data lock point

This section is for reporting any important new information received by the MAH since the database was frozen for review. It may include significant new cases or follow-up data that affect the interpretation or evaluation of existing adverse reaction reports. The impact of this information on the overall safety evaluation should be discussed.

7. Human Reactions to Veterinary Medicinal Products

Human adverse reaction: a reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine.(as defined in Article 1 (11) of Directive 2001/82/EC)

Information about any suspected adverse reactions (serious or non-serious) in humans, should be reported with the following details:

- i) Patient identification (as appropriate according to national laws)
- ii) Sex
- iii) Age or adult/child
- iv) Patient occupation - if relevant to exposure to the veterinary medicinal product
- v) Suspected veterinary medicinal product details [Brand name, MA number, active substance(s)]
- vi) Nature of exposure
- vii) Date of product use/exposure
- viii) Date(s) of reaction
- ix) Nature of adverse reaction including signs and symptoms
- x) Outcome of reaction
- xi) Name, address, telephone number of medical doctor/physician (or Poison Centre) if consulted

Suspected adverse reactions, to nationally authorised products, occurring in humans should be reported immediately, and in no case later than 15 days following receipt, to the competent authorities of the Member State (and the Agency for veterinary medicinal products with Community authorisations) in whose territory the incident occurred. Where not all the information is available at the time of sending the report the minimum information may be sent (see section 4.2) with a follow-up report to be sent later.

ANNEX I

Event Charts of Marketing Authorisation Holder Reporting Procedures

Event Chart of Marketing Authorisation Holder Reporting Procedures

Serious Suspected Adverse Reactions in **animals** after use of a Veterinary Medicinal Product

Where Serious SAR occurred	Type of Authorisation	Unexpected/ Expected	Where to report	When to report
In EU	National and Community	Unexpected and Expected	To MS where the adverse reaction occurred (and Agency if Community authorisation)	Within 15 days of single report receipt and later in relevant PSUR
Outside EU	National	Unexpected	To MS where product authorised	Within 15 days and in relevant PSUR
		Expected	To MS where product authorised – may not be necessary depending on requirements of marketing authorisation	In relevant PSUR ^t
	Community	Unexpected	To Agency and to all MS	Within 15 days of single report receipt and in later in relevant PSUR
		Expected	May not be necessary depending on requirements of marketing authorisation	In relevant PSUR

Unexpected adverse reaction – an adverse reaction which is not mentioned in the SPC.

Event Chart of Marketing Authorisation Holder Reporting Procedures

Non-Serious Suspected Adverse Reactions in **animals** after use of a Veterinary Medicinal Product

Where Non-Serious SAR occurred	Type of Authorisation	Unexpected/ Expected	Where to report	When to report
In EU	National and Community	Unexpected and Expected	To MS concerned and to the Agency if Community authorisation	In relevant PSUR
Outside EU	National	Unexpected	To MS where authorised	In relevant PSUR
		Expected	Not necessary	N/A
	Community	Unexpected	To Agency and to all MS	In relevant PSUR
		Expected	May not be necessary depending on requirements of authorisation	In relevant PSUR

Unexpected adverse reaction – an adverse reaction which is not mentioned in the SPC.

Event Chart of Marketing Authorisation Holder Reporting Procedures

Suspected Adverse Reactions in humans after use of a Veterinary Medicinal Product

Where SAR occurred	Type of Authorisation	Unexpected/ Expected	Where to report	When to report
In EU	National & Community	Unexpected & Expected	To MS where the reaction occurred and the Agency if Community authorisation)	Within 15 days of single report receipt and later in relevant PSUR (
Outside EU	National	Unexpected	To MS where the product is authorised	Within 15 days of single report receipt and later in relevant PSUR
		Expected	May not be necessary depending on the requirements of marketing authorisation	In relevant PSUR
	Community	Unexpected	To the Agency	Within 15 days of single report receipt and later in relevant PSUR
		Expected	May not be necessary depending on the requirements of marketing authorisation	In relevant PSUR

Unexpected adverse reaction – an adverse reaction which is not mentioned in the SPC.

TABLE A

European Veterinary Pharmacovigilance Reporting Form for MAHs

<p>Safety issues</p> <p style="padding-left: 20px;">in animals <input type="checkbox"/></p> <p style="padding-left: 20px;">in humans <input type="checkbox"/></p> <p>Lack of expected efficacy <input type="checkbox"/></p> <p>Withdrawal period issues <input type="checkbox"/></p> <p>Environmental problems <input type="checkbox"/></p>	<p>SENDER REPORT IDENTIFICATION – CASE REF. No:</p> <p>Reporting country:</p> <p>Purchase country:</p> <p>Report source:</p>	1				
<div style="border: 1px solid black; padding: 5px; display: inline-block; margin: 10px auto; width: 30%;">1. ADDRESS OF COMPETENT AUTHORITY</div>						
<p>Date complaint received by sender: (dd/mm/yy)</p> <p>Type of report: Initial <input type="checkbox"/> Follow-up <input type="checkbox"/> (date, case number)</p> <p>Person who reported the reaction: veterinarian <input type="checkbox"/> owner <input type="checkbox"/> physician <input type="checkbox"/> pharmacist <input type="checkbox"/> other:</p>						
<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;">3. VETERINARIAN / PHYSICIAN / PHARMACIST</div> <p>Name:</p> <p>Address:</p> <p>Telephone No.</p>	<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;">4. ANIMAL OWNER / HUMAN PATIENT</div> <p>Name <i>(according to the confidentiality legislation in EU country)</i>:</p> <p>Address:</p> <p>Telephone No.</p>					
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; border: 1px solid black; padding: 5px;">5. ANIMAL DATA</td> <td style="width: 25%;">No. of animals treated:</td> <td style="width: 25%;">No. of animals showing signs:</td> <td style="width: 25%;">No. of animals died:</td> </tr> </table> <p>Animal characteristics (animal(s) showing signs):</p> <p>Species: Breed/production type:</p> <p>Sex/physiological status: female <input type="checkbox"/> male <input type="checkbox"/> pregnant <input type="checkbox"/> neutered <input type="checkbox"/> lactating <input type="checkbox"/> other:</p> <p>Weight (kilos): Age:</p> <p>State of health at time of treatment: good <input type="checkbox"/> fair <input type="checkbox"/> poor <input type="checkbox"/> critical <input type="checkbox"/> unknown <input type="checkbox"/></p>			5. ANIMAL DATA	No. of animals treated:	No. of animals showing signs:	No. of animals died:
5. ANIMAL DATA	No. of animals treated:	No. of animals showing signs:	No. of animals died:			

Reason(s) for treatment (prevention against what disease(s) or initial diagnosis):

6. PRODUCT DATA # 1

M.A. number:

Trade name (include dosage form and strength):

Active substance(s) (INN):

ATC vet code(s):

Batch No.:

Expiry date:

Storage details:

Treatment details:

Dose/frequency:

Route/site of administration:

Start date of treatment:

Stop date or duration:

Who administered the product:

veterinarian owner other

Use according to label: yes unknown no explain:

Action taken after reaction: **drug withdrawn** **dose reduced** **other**

Did reaction abate after stopping drug ? yes no not applicable

Did reaction reappear after reintroduction ? yes no not applicable

List all other relevant medications given to animal(s):

Give the list of the other veterinary medicinal products used concurrently and go to special field for completion of details (page 3)

SENDER CASE REF. No:

2

7. REACTION DATA (applicable for all types of adverse reaction(s) reported following administration of veterinary product(s))

Date of onset of signs:

Duration of reaction:

Describe the sequence or events including administration of product(s), all clinical signs, site of reaction, severity, pertinent lab tests, necropsy results, possible contributing factors (if necessary use extra sheet): Include details of treatment given to address this adverse reaction.

Were the signs treated?

No

Yes

Outcome of reaction to date:

	Killed/euthanised	died	under treatment	alive with sequelae	recovered	unknown
No. of animals:						
Date when:						

8. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT PRODUCT #1 CAUSED REACTION

possible

unlikely

no attending vet

9. PREVIOUS EXPOSURE AND REACTION(S) TO PRODUCT #1

Previous exposure to this product? no yes Date(s):

Previous reaction to this product? no yes Describe:

De-challenge information:

10. DETAILS OF SUSPECTED ADVERSE REACTION(S) IN HUMANS

Patient details Sex: Age/date of birth: Occupation (with relevance to exposure):

Date of exposure: Date of reaction:

Nature and duration of exposure, reaction details (including symptoms) and outcome:

11. CAUSALITY ASSESSMENT RELATED TO PRODUCT #1

Classification: A (probable) B (possible) O (unclassified) N (unlikely)

Reason for classification:

12. OVERALL CAUSALITY ASSESSMENT RELATED TO ALL SUSPECTED PRODUCTS

FOR COMPETENT AUTHORITY USE ONLY

Name and title of person responsible for the accuracy of the information Signature Date

To replicate for each product used concurrently

SENDER CASE REF. No:	3
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6. DATA FOR PRODUCTS ADMINISTERED CONCURRENTLY – PRODUCT # <Enter sequential number; 2 or higher>

Trade name (include dosage form and strength):		M.A. number:
Active substance(s) (INN):		ATC vet code(s):
Batch No.:	Expiry date:	Storage details:
Treatment details:		
Dose/frequency:		Route/site of administration:
Start date of treatment:	Stop date or duration:	Who administered the product:
veterinarian <input type="checkbox"/> owner <input type="checkbox"/> other <input type="checkbox"/>		
Use according to label:	yes <input type="checkbox"/> unknown <input type="checkbox"/>	no <input type="checkbox"/> explain:
Action taken after reaction:	drug withdrawn <input type="checkbox"/>	dose reduced <input type="checkbox"/> other <input type="checkbox"/>
Did reaction abate after stopping drug?	yes <input type="checkbox"/> no <input type="checkbox"/>	not applicable <input type="checkbox"/>
Did reaction reappear after reintroduction?	yes <input type="checkbox"/> no <input type="checkbox"/>	not applicable <input type="checkbox"/>

8. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT REACTION WAS CAUSED BY PRODUCT #

possible unlikely no attending vet

9. PREVIOUS EXPOSURE AND REACTION(S) TO PRODUCT #

Previous exposure to this product? no yes Date(s):

Previous reaction to this product? no yes Describe:

De-challenge information:

11. CAUSALITY ASSESSMENT RELATED TO PRODUCT #

Classification: A (probable) B (possible) O (unclassified) N (unlikely)

Reason for classification:

IN CONFIDENCE

TABLE B

VETERINARY PHARMACOVIGILANCE SCHEME - PERIODIC SAFETY UPDATE REPORT

MARKETING AUTHORISATION HOLDER FORM FOR MULTIPLE REPORTS OF ANIMAL SUSPECTED ADVERSE REACTIONS

MARKETING AUTHORISATION HOLDER:

VETERINARY MEDICINAL PRODUCT:

MARKETING AUTHORISATION NO:

PERIOD OF REPORT: FROM .. /.. /.. TO .. /.. /..

No. OF DOSES SOLD DURING PERIOD OF REPORT:

ADVERSE REACTION INCIDENCE (%):

MAH CASE REF	DATE(S) OF TREATMENT(S)/ VACCINATION(S)	DATE OF REACTION	NO. TREATED	SPECIES AND AGE	NO. REACTED	NO. DEAD _e	WAS PRODUCT USED AS RECOMMENDED YES/NO	OTHER PRODUCTS USED CONCURRENTLY	PRESENTING SIGNS/ DIAGNOSIS	MAHs CAUSALITY ASSESSMENT (A B O N codes)	MAH COMMENTS
TOTAL											

FOR COMPETENT AUTHORITY USE ONLY

REFERENCE:

DATE OF RECEIPT:

Section 2: Guidance and Procedures for Competent Authorities

**2.1 GUIDELINE FOR COMPETENT AUTHORITIES FOR THE
VERIFICATION AND EVALUATION OF PHARMACOVIGILANCE
INFORMATION CONCERNING VETERINARY MEDICINAL PRODUCTS**

Legal Basis And Purpose

The legal framework for reporting, collecting, collating and evaluating pharmacovigilance data on veterinary medicinal products in the Community is contained in Directive 2001/82/EC and Council Regulation (EEC) No. 2309/93. Pharmacovigilance obligations apply to all authorised veterinary medicinal products.

Reports of suspected adverse reactions, as well as data on use (consumption) must be collated and scientifically evaluated by competent authorities of Member States of the Community.

Suspected human adverse reactions following use of veterinary medicinal products are also routinely transmitted to competent authorities and must be evaluated. Furthermore, for veterinary medicinal products with known side effects, the evaluation must take into account whether there is an increased incidence of such effects.

The pharmacovigilance systems in place should consider the available adverse reaction data following off-label use of veterinary medicinal products.

Potential environmental problems, suspected lack of expected efficacy or reported violations of approved residue limits that lead to the investigation of the validity of the withdrawal period, are aspects of post-authorisation surveillance which are also considered within the scope of veterinary pharmacovigilance.

Following the notification of individual adverse reactions reports either from the Marketing Authorisation Holders (MAHs) directly or from another concerned party to the Competent Authorities of suspected adverse reactions (SARs) to veterinary medicinal products, it is necessary to record and evaluate the report. Basic information on the SAR will have been established from the individual report. These details must be validated by checking the particulars with the reporter and/or other parties involved. In checking with the reporter, it is important to ensure consistency in scope and quality of the information gathered. Therefore, the accuracy of the particulars should be reaffirmed and omission of any details queried.

Periodic Safety Update Reports (PSURs) must also be reviewed by Competent Authorities both during the first years following the grant of the product authorisation and at time of renewal of the authorisation. Specific advice on the evaluation of PSURs is given in chapter 3 below.

The following sub-headings may be useful in the evaluation of a report:-

1. Details and particulars;
2. Causality assessment;
3. Action required.
4. Documentation of decision taken and notification of that decision to the MAH, to the other Member States concerned, to the Agency and if appropriate to the Commission, in accordance with the requirements laid down in Article 78 of Directive 2001/82/EC

1. Details and Particulars

To assist in the validation and assessment of the SAR, the format of particulars outlined in Table A of the previous sections should be followed.

Where complete information on a report is submitted by the Marketing Authorisation Holder (MAH), the Competent Authority may be in a position to evaluate the information without need for further

clarification. In these cases the Competent Authority should verify the record(s) by a system of random checks on records. In those cases where the report is notified by the veterinarian, pharmacist or other animal health professional or animal owner directly to the Competent authority and not indirectly via the MAH, the information should always be verified by the Competent authority.

1.1 Veterinary Medicinal Product Details

Details of the composition of the veterinary medicinal product including vehicle and excipients should be recorded together with the batch number(s) of the relevant product if available. Where the veterinary medicinal product has a marketing authorisation, it is necessary to establish whether the product was used within the terms of the authorisation. In many cases, it will also be useful to clarify the immediate previous use of the veterinary medicinal product itself or batch, and whether other products (including feed additives) were administered, prior to or together with the suspected veterinary medicinal product. Where more than one veterinary medicinal product was used, full particulars of each veterinary medicinal product should be documented.

1.2 Animal Details

While details of the number of treated animals, the number reacting and the number of deaths will be established from the original report form, it may be necessary to obtain further details on the report including information on the condition of the animal before treatment, the reason for treatment, the pregnancy state, recovery details and any other pertinent information available to facilitate assessment of the case. Where an animal has died, information from post mortem reports should be obtained if available. Reports of laboratory or other investigations should also be sought where appropriate.

To ensure that the same report is not duplicated, it is necessary that the specific address of the farm/location where the suspected adverse reaction occurred and/or the reporter of the reaction be documented. However, as many criteria as possible should be used to check for duplicates.

1.3 Human Adverse Reactions to Veterinary Medicinal Products

Where suspected adverse reactions in humans following exposure to a veterinary medicinal product are reported, it may be necessary to contact the investigating medical doctor or national poison/toxicology investigation centre to clarify details of the report. Whilst recognising that it may be difficult to obtain medical information concerning a patient it is nevertheless important to capture the following minimum details:

- i) Patient identification (as appropriate according to national laws)
- ii) Sex
- iii) Age or adult/child
- iv) Occupation - if relevant to exposure to veterinary medicinal product
- v) Nature of exposure (e.g. inhalation, injection, ingestion or dermal exposure)
- vi) Nature of adverse reaction including signs and symptoms
- vii) Date of veterinary medicinal product used
- viii) Date of adverse reaction
- ix) Outcome of adverse reaction (e.g. extent of recovery, specific treatment required)
- x) Name, address, telephone number of medical doctor/physician (or Poison Centre) if consulted.

2. Causality Assessment

An assessment of causality should be made on each adverse reaction report submitted. Various approaches to assign causality are possible. However, in order to exchange data for European Community purposes four categories of conclusions can be made:

Category “A” : **Probable**

Category “B” : **Possible**

Category “O” : **Unclassified** (cases where insufficient information was available to draw any conclusion)

Category “N” : **Unlikely** to be product related (cases where sufficient information was available and where investigation has established this beyond reasonable doubt).

In assessing causality the following factors should be taken into account:

1. associative connection, in time which may include dechallenge and rechallenge following repeated administration or in anatomic sites
2. pharmacological explanation; blood levels; previous knowledge of the drug.
3. presence of characteristic clinical or pathological phenomena
4. exclusion of other causes
5. completeness and reliability of the data in the case reports
6. quantitative measurement of the degree of contribution of a product to the development of a reaction (dose-effect relationship).

For inclusion in category “A” (probable) it is recommended that all the following minimum criteria should be complied with:

1. There should be a reasonable association in time between the administration of the veterinary medicinal product and onset and duration of the reported adverse reaction.
2. The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology profiles of the veterinary medicinal product.
3. There should be no other equally plausible explanation(s) of the case. (If such are suggested - are they validated? What is their degree of certainty?). In particular, concurrent use of other products, and possible product interactions, or intercurrent disease should be taken into account in the assessment.

Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information) then such reports can only be classified as “B” (possible), “N” (unlikely) or “O” (unclassifiable/not assessable).

For inclusion in category “B” (possible), it is recommended that this be applied when drug causality is one (of other) possible and plausible causes for the described event but where the data does not meet the criteria for inclusion in category “A”.

In cases where sufficient information exists to establish beyond reasonable doubt that product causality was not likely to be the cause of the event then such reports should be classified as “**N**” (**unlikely**).

Where reliable data concerning an SAR is unavailable or is insufficient to make an assessment or causality then such reports should be classified as “**O**” (**unclassifiable/not assessable**).

The causality assessment made by the Competent Authority may differ from that of the Marketing Authorisation Holder. If this is the case, the competent authority should when possible communicate its conclusion and the reason(s) for the decision to the Marketing Authorisation Holder.

3. Periodic Safety Update Reports(PSURs)

Periodic safety update reports of world-wide experience, provided at defined times post authorisation, must be evaluated to ascertain whether further investigations need to be carried out and/or whether changes should be made to the Summary of Product Characteristics, labelling or packaging.

From the information on volume of sales provided, the incidence of adverse reactions will have been documented in the report. However, theoretical calculations for single species, though arbitrary, may be of some value.

The competent authority should cross-check that:

- * All individual serious reports previously notified to them are included in the PSUR.
- * Reports sent directly from veterinarians, pharmacists and other healthcare professionals, who indicated that the information would also be sent to the Marketing Authorisation Holder (MAH), are included in the PSUR.
- * All relevant bibliography known to the competent authority is included.
- * An overall safety evaluation of the risk/benefit profile of the veterinary medicinal product has been provided by the MAH.

The competent authority should evaluate the data provided and verify whether the information provided remains in line with risk/benefit analysis conducted at time of granting the authorisation. If the evaluation of the information provided in the PSUR leads to a change in the risk/benefit ratio, the competent authority should clearly document this in an addendum to the original assessment report.

4. Action required for individual Suspected Adverse Reaction Reports

The date of receipt of the adverse reaction report should be logged by the Competent Authority. Following the validation of the adverse reaction report, it should be recorded and a letter of acknowledgement sent to the reporter.

The Competent Authority should clarify whether the MAH has been informed and if not, notify the MAH of the given veterinary medicinal product, within 15 days that a report has been received. While the primary responsibility for any action to be taken rests with the MAH, nevertheless, depending on the nature and frequency of the adverse reaction, the competent authority will decide on a course of action. In the case of adverse reaction reports which have been assigned a causality assessment code, ‘A’ or ‘B’, this may include:-

- (a) To discuss with the MAH the nature, frequency and, if possible, the mechanism of the SAR (e.g. allergic, toxic, microbiological), and establish what action might be taken.
- (b) To await the result of the MAH investigation including, where relevant, details of batch analysis.

- (c) If appropriate, to carry out independent analysis on the suspect veterinary medicinal product and/or a veterinary medicinal product from the same batch.
- (d) To subject the veterinary medicinal product to more frequent monitoring by requesting the MAH to provide, at regular intervals, an additional periodic safety update report..
- (e) To request the MAH to carry out a risk/benefit analysis on the product with particular reference to the adverse reaction experience and the volume of sales of the veterinary medicinal product or unit treatments given for the period under review.
- (f) To transmit to the Pharmacovigilance Working Party, Committee for Veterinary Medicinal Products information about regulatory action to be taken or envisaged.
- (g) To transmit to the Agency all cases related to veterinary medicinal products authorised through the centralised procedure, in no case later than 15 days following the receipt of the information.
- (h) After informing the MAH of the reasons for the regulatory action adopted and discussion with the MAH whenever possible,
 - to issue or to instruct the MAH to issue a mail shot or notice to veterinarians or other users with data concerning a side effect,
 - to instigate a rapid alert procedure,
 - to effect a batch or product recall via the MAH.

It should be noted that reports of suspected serious adverse reactions (which have been assigned causality assessment code of 'A' or 'B'), must be notified to the Agency immediately or at the latest within 15 days.

5. Documentation of decision taken and Notification of that decision

All decisions taken by Competent Authority and the reasons for those decisions should be documented. Where a decision is made to withhold, withdraw or suspend authorisation to manufacture, import or market a veterinary medicinal product, the party concerned shall be notified and informed of the alternative products available under current legislation and of the time allowed for seeking such alternative products. The Agency shall also be informed of such decisions, together with the reasons on which the decisions are based.

6. Stimulating reporting of SAR Reports

While, in order to respect the confidentiality of veterinary medicinal product information, the generic name of the active or inactive substance contained in the veterinary medicinal product should be used in any report intended for the public, nevertheless, when justified in the opinion of the competent authority, the proprietary name of the veterinary medicinal product linked to the suspected adverse reaction may be given. In order to encourage the voluntary notification of suspected adverse reactions, it is useful to collate and summarise the adverse reaction reports validated as probable ("A") or possible ("B") and to make this information available to the concerned professionals in a relevant manner. Direct contact with veterinarians, pharmacists and veterinary investigative laboratories, as well as organisations representing these individuals is advocated. Other means of encouragement, e.g. by placing advertisements in relevant journals or participating in discussions at Veterinary Colleges and targeting new graduates in particular, as well as stimulating research in the area of veterinary pharmacovigilance are also useful. Ongoing encouragement of reporting is necessary and annual reporting of the experience of competent authorities to the concerned professionals is desirable.

**2.2 CONDUCT OF PHARMACOVIGILANCE FOR VETERINARY MEDICINAL
PRODUCTS AUTHORISED THROUGH THE MUTUAL RECOGNITION
PROCEDURE**

1. Introduction

The objective of this paper is to develop a framework whereby all veterinary medicinal products authorised through the procedure of Mutual Recognition (MR) are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken. Veterinary medicinal products covered by these procedures include those authorised through mutual recognition, ex-concertation products and those referred under Articles 35, 39, 40 and 41 of Directive 2001/82/EC.

The process of MR is facilitated by the Veterinary Mutual Recognition Facilitation Group (VMRFG). It acts to support the development of consensus where differences of opinions arise so as to minimise the need for arbitration. For practical reasons, the Committee for Veterinary Medicinal Products (CVMP) and its Pharmacovigilance Working Party (PhVWP) advise Member States (VMRFG) on issues of scientific relevance. It should however be noted that this facilitation mechanism in no way changes the legal obligations for reporting of adverse reactions by all parties concerned nor for referrals to the CVMP as appropriate.

Because of the need to co-ordinate the process of pharmacovigilance and any consequential regulatory action across all relevant Member States, a standard operating procedure for the conduct of pharmacovigilance for MR veterinary medicinal products is necessary; this should reduce duplication of work and facilitate harmonisation between Member States.

This chapter presents:

- The principles relevant to the conduct of pharmacovigilance for MR veterinary medicinal products.
- a procedure for the conduct of pharmacovigilance for these mutually recognised veterinary medicinal products.
- the specific roles of the different parties involved in carrying out these pharmacovigilance functions

The procedures outlined in this document apply once a veterinary medicinal product has entered the MR procedure or falls within it by virtue of being part of the concertation procedure or following referral under Articles 35, 39, 40 and 41..

2. Legal framework

Directive 2001/82/EC and Commission Regulation (EC) No. 1084/2003 , set the basis for the authorisation and variation of veterinary medicinal products through the MR procedure and for pharmacovigilance thereafter.

Pharmacovigilance procedures and obligations of Marketing Authorisation Holders (MAH), competent authorities and the Agency, which includes the CVMP and the secretariat are outlined in this volume., Commission Regulation (EC) No. 1084/2003 provides the legislative basis for variation of MR marketing authorisations including urgent safety restrictions.

3. Principles and parties involved

The responsibilities and functions of the various partners involved in the MR procedure are defined in the legislation for the handling of marketing authorisations and subsequent variation applications. Although there are no equivalent legislative procedures defined for the handling of pharmacovigilance issues which arise for veterinary medicinal products which have been authorised by mutual recognition, Member States have agreed that similar principles should also be applied to the conduct of

pharmacovigilance for MR products, with the Reference Member State (RMS) taking the lead in pharmacovigilance in close co-operation with Concerned Member States (CMS). The role of the relevant parties is presented below:

Reference Member State (RMS)

For practical reasons Member States have agreed that the RMS should be assigned responsibility for evaluating all pharmacovigilance issues relevant to a MR veterinary medicinal product, for providing assessment reports to the CMS to an agreed timetable and presenting the issues which need to be considered as appropriate by the Veterinary Pharmacovigilance Working Party (PhVWP). The RMS will be responsible for liaising with the MAH on all such matters. In cases where the original RMS expresses its inability to carry out these functions, another MS may be assigned to act as RMS. In situations where a class-related effect is identified for products with different RMS, a “lead” RMS may be appointed by agreement between the relevant RMS to take forward evaluation of the class-related effect.

Concerned Member State (CMS)

Competent authorities of all CMS have a responsibility to continuously collect information on adverse reactions and play an important role in identifying and evaluating possible alerts of product safety hazards for MR products. The CMS will work closely with RMS on such issues, and will respond to proposals from RMS within the agreed timetable.

Competent Authorities

All competent authorities are responsible for ensuring implementation of regulatory action in their territory. The PhVWP facilitates co-ordination of pharmacovigilance of MR products across Member States (CMS and RMS) and the development of consensus to reach conclusions and agree proposed actions where differences arise between Member States.

Veterinary Pharmacovigilance Working Party (PhVWP)

The PhVWP facilitates co-ordination of pharmacovigilance of MR products across Member States and the development of consensus on conclusions and proposed actions. The PhVWP will be the forum for discussing all pharmacovigilance issues relevant to mutually recognised veterinary medicinal products. The present mandate of the PhVWP encompasses consideration of pharmacovigilance issues at the request of the CVMP and at the request of Member States. These issues are addressed as clearly defined separate parts of the PhVWP agenda.

Veterinary Mutual Recognition Facilitation Group (VMRFG)

The VMRFG will be kept closely informed on issues relevant to it i.e. variations for safety reasons by the provision of the minutes of the PhVWP and the attendance of the PhVWP chairperson at the VMRFG on invitation as appropriate..

Agency secretariat and CVMP

The CVMP becomes involved in issues relevant to MR products whenever there is a procedure according to Directive 2001/82/EC Article 39, 40 or 41. The Agency secretariat accept to (1) provide administrative support to the PhVWP, (2) co-ordinate all activities in the event of referral to the CVMP and (3) be kept informed according to Directive 2001/82/EC Articles 36 and 39.

European Commission

The European Commission is the competent authority for the adoption of any decision relating to veterinary medicinal products which have been adopted as a result of referrals according to Article 35 and 40 of Directive 2001/82/EC.

Marketing Authorisation Holders (MAH)

The MAH is obliged to adhere to the legal requirements of pharmacovigilance (spontaneous reporting of adverse reactions, submission of PSURs and other information) for MR products as for any other centrally or nationally authorised products.

Member States have agreed that the RMS will act as the primary liaison with the MAH, specifying issues requiring clarification, further information or specific actions by the MAH. This will be clearly presented in writing to the MAH by the RMS working closely with CMS. Meetings with the MAH should involve the RMS, and any other CMS by request. The conclusions of such meetings should be distributed to the PhVWP members and members of VMRFG.

4. Functions and Procedures

4.A Reporting, Distribution and Evaluation of Information relevant to Pharmacovigilance of Mutually Recognised veterinary medicinal products

1. During the process of consideration of a MR Application

In the interim time between an application for a marketing authorisation through the MR procedure and completion of this process, information relevant to the safety of the product may become available from the applicant, or Member States or third countries where the veterinary medicinal product is already authorised and marketed. Since it is essential for this information to be included in the risk/benefit evaluation, the applicant is responsible for immediately informing the RMS and the other CMS of such an information. The RMS will assess whether this new information modify the overall assessment, releasing an amended assessment report as appropriate.

2. After completion of the MR Authorisation

2.1 Spontaneous single case reports

All Member States competent authorities have spontaneous adverse reactions reporting schemes whereby veterinarians, others professionals and MAH report suspected adverse reactions to veterinary medicinal products. Directive 2001/82/EC lays down specific obligations on Member States competent authorities and MAH on the expedited reporting of Suspected Adverse Reactions (SAR). The Competent Authorities in Member States are responsible for collecting, collating and evaluating reports occurring in their respective territory. Those reports from outside the EU are sent by the MAH to all CMS, however Member States have assigned responsibility to the RMS to collate and to evaluate those reports. It is particularly important for the RMS responsible for the overall pharmacovigilance evaluation of a MR veterinary medicinal product to have access to all of the relevant information.

2.2 Periodic Safety Update Reports (PSURs) and other relevant post-authorisation information

The MAH is required to provide all competent authorities with PSURs and relevant safety information from post-authorisation commitments, post-authorisation studies, world literature, or other sources as outlined in the Directive 2001/82/EC and guidance for MAH. Any consequential variation should be submitted by the MAH at the same time. RMS has agreed to evaluate the information, to identify any

possible hazard, and to circulate an assessment report to the CMS within 6 weeks of receipt. CMS should respond within 3 weeks of receipt of the RMS assessment report. This assessment report will, if requested by the RMS or CMS, be discussed at a PhVWP meeting, with the agreement of the CVMP.

2.3 Alert generation

It is possible that pharmacovigilance alert will emerge in the early stages of the marketing of a MR veterinary medicinal product especially for a new active substance. It will be important for these alerts to be evaluated effectively. An alert of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may be identified from many different sources of information by the MAH, the RMS, or any CMS.

It is the responsibility of each Member State to identify pharmacovigilance alert issues from information arising in its territory. However, it will be important for the RMS to have the totality of information in order to have an overall view of the experience gathered in relation to the concerned MR veterinary medicinal product. As a matter of routine, the RMS should continually evaluate all newly submitted information in the context of information already available on the veterinary medicinal product, to determine the emerging adverse reaction profile. The RMS should request additional information from the MAH as necessary. The PhVWP should regularly review emerging safety issues.

2.4 Risk evaluation

As alerts of possible unexpected hazards or changes in the severity, characteristics or frequency of expected adverse reactions emerge, the relevant information needs to be brought together for effective evaluation over a time scale appropriate to the importance and likely impact of the alert.

Any risk evaluation prompted by a signal should normally be carried out by the RMS unless other arrangements are agreed with another MS e.g. the CMS where the original signal was identified in the case of a rapid alert when an assessment report has had to have been prepared. The RMS should in any case work closely with the originator of the signal. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the RMS or the originator MS, or jointly. Assessment reports may be discussed at the PhVWP as necessary on request of the RMS or CMS.

Any other Member State than the RMS should not start a full evaluation prior to having contacted the RMS, in order to prevent any unnecessary duplication of work.

2.5 Tracking of pharmacovigilance issues

A tracking system for pharmacovigilance issues relevant to MR products will be set up - called the "MR VetDrug Monitor". It will record actions that arise from investigated signals PSURs, specific obligations and follow-up measures and will be reviewed at each PhVWP. The RMS for a particular veterinary medicinal product has agreed to be responsible for ensuring the monitor is fully up-to-date for that veterinary medicinal product and providing the relevant information to the Agency secretariat.

4.B Proceedings in Case of Safety Concerns

1. Hazards During the Ongoing MR Process

If in the course of the MR process and following the assessment of all information relevant to the safety of a veterinary medicinal product the RMS considers that a significant risk has emerged to change the benefit/risk balance, the outcome of the evaluation should be discussed at the PhVWP and be taken into account in any ongoing MR procedure within the VMRFG.

2. Hazards after MR Authorisation

2.1 Non-urgent safety issues

Potential concerns that do not fulfil the criteria for a Rapid Alert should be brought to the attention of the RMS. The RMS may request further information from the CMS or the MAH. The RMS should work closely with the MS who identified the issue to evaluate the matter. Agreement needs to be reached in each case on the responsibility of evaluation of the issue by RMS or originating CMS, or jointly. Following evaluation, the need for further discussion at the PhVWP will be at the request of the RMS or CMS.

2.2 Urgent safety issues

For urgent issues the Rapid Alert System should be used by the RMS or the other MS when a signal is detected which leads to concern about the risk/benefit of a MR veterinary medicinal product and which could lead to major changes in the status of that authorisation. The Rapid Alert should be transmitted to the contact points of the RMS, the CMS, the European Commission and the Agency secretariat. The MAH should also be informed. The RMS should work closely with the originator of the alert to evaluate the matter. [See also Part 3, chapter 2.3 Rapid Alert System (RAS) and Non Urgent Information in Veterinary Pharmacovigilance.]

The RMS will prepare a risk/benefit assessment report based on the assessment report of the MS, which issued the rapid alert and also decides which additional information is to be requested from the MAH and CMS. Following risk evaluation a discussion should be held at the PhVWP aimed at reaching agreement between RMS and CMS. In cases of particular urgency a special meeting of the PhVWP may be convened. Any member State (RMS or CMS) may initiate immediate suspension of the marketing authorisation if considered necessary (see 3.2).

3. Actions consequential to Safety concerns

Safety issues are likely to emerge from the many sources of information considered above which warrant amendment to the conditions of the marketing authorisation, usually through the process of variation. In the case of serious risk, which is considered to outweigh the benefit of a product, there may be a need to withdraw the product from the market. Such actions may be taken voluntarily by MAH or compulsorily by competent authorities.

3.1 Action by the Marketing Authorisation Holder

Variations of the marketing authorisation submitted by the MAH because of safety concerns should be handled through the normal variation procedures for MR products with the RMS evaluating the variation and circulating an assessment report of the CMS within the normal time scale.

In the case of a MAH wishing to withdraw its marketing authorisation, action needs to be co-ordinated across the CMS by the RMS, including communication to veterinarians.

3.2 Action by the Competent Authorities

If following risk evaluation by the RMS it is considered that action is necessary to vary, suspend or withdraw the terms of the marketing authorisation of a veterinary medicinal product, the RMS should inform the CMS.

It is essential to ensure a co-ordinated approach, efforts should be made to reach a consensus on the proposed action to be taken, through discussion within the PhVWP.

Where appropriate the RMS should communicate with the MAH on the reasons for the conclusions reached by the MS and the action that should be taken by the MAH. If the MAH does not propose to

voluntarily vary, suspend or withdraw the MA, a referral according to Articles 35, 40 or 41 of Directive 2001/82/EC, to the CVMP is necessary. In these cases, reference should be made to the standard operating procedures on referrals in accordance with the provisions of Directive 2001/82/EC in the case of safety concerns related to veterinary medicinal products marketed in the European Union. The resulting CVMP opinion will be followed by a single decision of the European Commission binding on all Member States. In urgent cases where a serious risk to public or animal health is reported, any Member States may initiate immediate suspension of the marketing authorisation of a veterinary medicinal product informing all the other Member States, the European Commission and the Agency secretariat within **24 hours**. Such action should preferably be taken in all Member States in a co-ordinated manner facilitated by a proposal from the CVMP and its PhVWP to the concerned competent authorities of Member States.

3.3 Communication to veterinarians, others concerned professionals and the general public

Veterinarians, others concerned professionals, and if considered appropriate, the general public may need to be informed about safety issues related to MR veterinary medicinal products. It is important that consistent information is provided in all Member States.

In such cases, the RMS should propose the content of the information to be provided, and whenever possible, this should be agreed by the CMS and, if appropriate considered by the PhVWP. There should be agreement whenever possible, on the method and timing of communication of the information e.g. by letters from MAH or Member States' competent authorities, or through competent authorities' bulletins. Agreement should also be reached on the need and timing of press statements and the reaction to press enquiries.

**2.3 RAPID ALERT SYSTEM (RAS) AND NON URGENT INFORMATION SYSTEM
(NUIS) IN VETERINARY PHARMACOVIGILANCE**

Background

The revision of the guidance in this chapter was considered necessary to reflect in particular the new developments in the field of information technology with regard to the efficient electronic exchange of Rapid Alerts and Non-Urgent Information.

1. Introduction

During the marketing period of a veterinary medicinal product urgent measures to safeguard animal or public health or the environment may be necessary. Within the European system of pharmacovigilance it is essential that information concerning safety hazards possibly resulting in major changes to the marketing authorisation status or withdrawal of a product, is exchanged between the Member States, the Agency and the European Commission (EC) with the appropriate degree of urgency.

An early exchange of information will enable the competent authorities of Member States to initiate data research and seek specialist expertise so that necessary decisions may be taken as soon as possible.

To support the rapid notification of safety concerns and the exchange of information required to take the necessary decisions, the competent authorities of Member States and European Free Trade Association (EFTA) countries concerned (Iceland, Liechtenstein and Norway), the Agency and the European Commission operate the Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in accordance with the procedure laid down in the guidance in this chapter.

In the event that a recall of a veterinary medicinal product or a product batch is necessary, the procedures outlined in the document, *Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects* published in the *Compilation of Community procedures on administrative collaboration and harmonisation of inspections*, as updated shall NOT apply.

2. Purpose

The purpose of the **Rapid Alert System (RAS)** is to alert, with the appropriate degree of urgency, other Member States, EFTA countries concerned, the Agency and the European Commission about newly available pharmacovigilance data for veterinary medicinal products which indicate that action could be needed urgently to protect animal or public health. It is essential that communication of such a problem occurs at an early stage, normally before a decision is taken in a member state.

The **Non Urgent Information System (NUIS)** is established to support the collection and exchange of pharmacovigilance information between the competent authorities of Member States, the European Commission and the Agency which does not fulfil the criteria for a Rapid Alert.

In both cases, the RAS and the NUIS, the issue may then be discussed in a broad manner

- at the CVMP Veterinary Pharmacovigilance Working Party on the basis of an assessment report,
- in the CVMP,
- or formalised within procedures laid down in Articles 35 and 36 Directive 2001/82/EC or Article 40 of Council Regulation (EEC) No. 2309/93 as amended.

3. Scope

The RAS should primarily be used in problems or concerns relating to **safety and efficacy** concerns of veterinary medicinal products authorised according to

- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products,
- Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended.

The system must not be saturated by the exchange of less urgent information. For this purpose the Non-Urgent Information-System should be used.

4. Criteria

4.1 Rapid Alert System (RAS)

The RAS should be used when a member state has concern about a change in the balance between risks and benefits of a veterinary medicinal product that could require major changes in the status of the marketing authorisation such as:

- the urgent variation, suspension or withdrawal of the marketing authorisation,
- the recall of the veterinary medicinal product from the market,
- changes in the Summary of Product Characteristics (SPC) such as¹⁹
 - the introduction of new contraindications,
 - the introduction of new warnings,
 - the reduction in the recommended dose,
 - the restriction in the indications,
 - the restriction in the availability of the veterinary medicinal product and
- the need to inform all animal health professionals (e.g. Veterinarians, pharmacist, others concerned professionals etc) about an identified risk without delay.

Concerns about a change in the risk benefit balance of a veterinary medicinal product or an active ingredient authorised according to Directive 2001/82/EC or Council Regulation (EEC) No. 2309/93 may be based on:

- a series of report(s) of unexpected and serious suspected adverse reactions ,
- reports of an expected adverse reactions which suggest greater severity or long-term sequelae than known or which identify new risk factors,
- significant increase in the reporting rate of expected serious adverse reactions

¹⁹ With regard to Article 78 of Directive 2001/82/EC, these criteria define a significant variation of the SPC.

- evidence from studies (clinical trials or epidemiological studies) indicative of unexpected risk or a change in frequency or severity of a known risk,
- knowledge that the efficacy of a veterinary medicinal product is not established as assumed to date,
- evidence that the risks of a particular product are greater than alternatives with similar efficacy.

4.2 Non Urgent Information System (NUIS)

For the exchange of potential pharmacovigilance alerts that do not fulfil the RAS criteria as defined above, the NUIS should be used. It refers e.g. to

- Pharmacovigilance data, which do not require immediate or urgent action and/or where additional information is required from other Member States to support the evaluation of a potential concern,
- Provision of pharmacovigilance information, which does not require a response.

5. Procedure

Normally the case relating to the suspicion or concern is formulated by one member state after evaluation of the data available in that member state or the receipt of any other relevant important information that should be shared with other Member States, the EFTA countries concerned, the Agency and the European Commission. This should also include any action initiated by the Marketing Authorisation Holder(s)

5.1 Sending a Rapid Alert or a Non-Urgent Information

In accordance with Article 46 of Council Regulation (EEC) No. 2309/93 as amended, the Agency, in consultation with Member States and the European Commission, has set up a data-processing network (EudraNet) for the rapid transmission of data between the Community competent authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding veterinary medicinal products marketed in the Community.

Following the successful piloting between Member States, the European Commission and the Agency, the electronic submission shall replace the Telefax system used previously to exchange that information. However, in case of urgency e.g. EudraNet access is not available or the network is down, the former Telefax system should be used as an alternative communication channel. The electronic communication with partners that are not connected via EudraNet has to be performed in a way that guarantees security and confidentiality of the data exchanged.

The establishment of pre-defined data formats is essential to ensure the collection of similar data, aid in exchange of information among the Member States, and assist the common evaluation. Proposed forms are enclosed with the guidance in this chapter. Templates are available on the EudraNet homepage <http://eudranet.eudra.org/> and can be accessed via the established Pharmacovigilance domain.

To send the form, the established Rapid Alert (RA) or NUI (Non Urgent Information) address lists (Veterinary RA + Veterinary NUI) and e-mail boxes should be used which refer to the contact points within the competent authorities of Member States, the Agency and the European Commission . The EudraNet E-mail policy IT-SOP 9724 in the latest version applies accordingly.

If using the RAS/NUIS the Member State should comply with the following rules:

- a) The template chosen must comply either with the Rapid Alert or the Non-Urgent Information System criteria.
- b) Clear and concise information on the reasons for the Rapid Alert/Non-Urgent Information should be provided so that there is no need for clarification in the first instance.
- c) The competent authority generating the Rapid Alert/Non-Urgent Information should transmit at least the minimal data listed in Annex I and template A.
- d) Any information required from recipients should be specified clearly.
- e) In the event a Telefax is sent it should be preferably typewritten; the size of the letters should be large enough to ensure that the text is satisfactory readable.
- f) Annexes to the RAS/NUIS, considered to give sufficient details where necessary, should also be transmitted electronically, if available. The format to be used is the one specified in the EudraNet E-mail policy IT-SOP 9724 in the latest version. In case, the annexes are not available electronically, the form should be completed including a reference that the referred annexes would be submitted separately via Telefax; the form should be sent via the defined address list to the dedicated mailboxes. A print out of this completed form should be attached to the faxed annexes.
- g) The Rapid Alert should be transmitted in case of a veterinary medicinal product authorised according to
 - *Directive 2001/82/EC* – nationally authorised veterinary medicinal products including those authorised through the mutual recognition procedure - *to the contact points of the Member States, the EFTA countries concerned, the Agency and the European Commission* ,
 - *Council Regulation (EEC) No. 2309/93 as amended* – centrally authorised medicinal products - *to the contact points of the Member States, the EFTA countries concerned, the Agency, the European Commission and the Rapporteur.*
 - *The Rapid alert should in any case also be provided to the chairman of the CVMP.*
- h) Non-Urgent Information should be transmitted in case of a veterinary medicinal product authorised according to
 - *Directive 2001/82/EC*– nationally authorised veterinary medicinal products -*to the contact points of the Member States, the EFTA countries concerned, the Agency and the European Commission,*
 - *Directive 2001/82/EC* - veterinary medicinal products authorised nationally through the mutual recognition procedure - *to the contact points of the RMS, all other Member States, the EFTA countries concerned, the Agency and the European Commission* ,
 - *Council Regulation (EEC) No. 2309/93 as amended* – centrally authorised veterinary medicinal products - *in the first instance only to the Agency and the Rapporteur. The originator of the issue and the Rapporteur may request further information from other Member States.*

- *The Non-Urgent Information should in any case also be copied to the chairman of the CVMP.*
- i) If the fax is used it has to be transmitted to the established contact points as indicated above. A list of the fax numbers will be also accessible on the EudraNet homepage. Changes related to the fax numbers should be notified to the Agency, the European Commission and the contact points in Member States and the EFTA countries concerned, immediately.
 - j) In case of urgency, when the member state concerned has suspended the marketing authorisation of a veterinary medicinal product or withdrawn the product from the market in order to protect animal or human health or the environment, the Agency, the European Commission, all Member States and the EFTA countries concerned have to be informed **at the latest on the following working day**.
 - k) When a Rapid Alert is circulated
 - *Related to a veterinary medicinal product authorised according to Directive 2001/82/EC – nationally authorised veterinary medicinal products - the initiating member state should inform the MAHs concerned in his country adequately and promptly. Receiving member States are responsible for informing MAH(s) in their own country. Information on the MAH(s) may be given via associations of the MAHs both in the sending and receiving member state.*
 - *Related to a veterinary medicinal product authorised according to Directive 2001/82/EC – veterinary medicinal products authorised nationally through the mutual recognition procedure - the RMS should inform the MAH adequately and promptly.*
 - *Related to a veterinary medicinal product authorised according to Council Regulation (EEC) No. 2309/93 as amended – centrally authorised veterinary medicinal products - the Agency secretariat in agreement with the Rapporteur will promptly start an inquiry and information exchange with MAH(s).*
 - l) According to the guidance in Part 2, chapter 2.6 on the *Principles of Providing the World Health Organisation with Pharmacovigilance Information* Rapid Alerts will be sent for non-centrally authorised veterinary medicinal products by the Member States and for centrally authorised products by the Agency in agreement with the European Commission if definitive measures related to the marketing authorisations of veterinary medicinal products (restriction, variation, suspension, withdrawal) are implemented by the competent authority or if the rapid alert informs about a public statement (positive or negative) made by the competent authority.

5.2 Responses to a Rapid Alert or Non-Urgent Information

Responses to a specific Rapid Alert should be sent only to the originating member state and the Agency no later than one week of receipt of the alert.

In case of a Non-Urgent Information requested answers should be provided to the originating member state and the Agency within the time frame indicated by the originator.

The template (see template B) to be used is the "ANSWER TO RAPID ALERT/NON-URGENT INFORMATION". The information requested by the generating member state should be provided.

The Agency will summarise the issues related to Rapid Alerts and Non-Urgent Information in the Drug Monitor, which will be discussed and updated at each meeting of the Pharmacovigilance Working Party.

5.3 Assessment of a Rapid Alert

An interim assessment report should be prepared within five weeks after transmission of the initial Rapid Alert

- For veterinary medicinal products authorised according to Directive 2001/82/EC – *nationally authorised veterinary medicinal products* – by the originating member state taking into account all information received and collated from other Member States,
- For veterinary medicinal products authorised according to Directive 2001/82/EC – *veterinary medicinal products authorised nationally through the mutual recognition procedure* - any risk evaluation should normally be carried out by the RMS unless other arrangements are agreed with Member States. In each case agreement needs to be reached on the responsibility for the management of the alert and the risk/benefit assessment by the RMS, or originator CMS, or jointly.
- For veterinary medicinal products authorised according to Council Regulation (EEC) No. 2309/93 as amended – *centrally authorised veterinary medicinal products* - the Rapporteur should work closely with the originator of the rapid alert to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or the originating member state, or jointly.

When the collated information provides evidence of a serious safety concern, a full risk/benefit assessment report for consideration by the veterinary Pharmacovigilance Working Party and/or CVMP should be prepared.

The assessment report should follow the format and content of the guideline on Pharmacovigilance assessment reports (Annex II) and used the template (Annex III).

The assessment report should be sent to all competent authorities in Member States, the EFTA countries concerned, the Agency and the European Commission and should be discussed at the next meeting of the veterinary Pharmacovigilance Working Party.

The assessment report should be distributed electronically using the defined Vet-Pharmacovigilance address list and the established e-mailboxes as indicated in the EudraNet E-mail policy, latest version. The electronic communication with partners that are not connected via EudraNet has to be performed in a way that guarantees security and confidentiality of the data exchanged. Consideration will need to be given to whether the matter is of Community interest and should be referred under Article 35 and 36 of Directive 2001/82/EC.

5.4 Assessment of Non-Urgent Information

On the basis of the Drug Monitor the veterinary Pharmacovigilance Working Party will discuss all topics exchanged via the Non-Urgent Information System and will agree on a case to case basis how to process the issue. In the event of the preparation of an assessment report is considered necessary the same assessment procedure applies as indicated for a Rapid Alert (chapter 5.3).

Annex I

Information for transmission of information about detected alerts Minimal data that should be filled in every case

1. Identification:

- Type of message categories: Rapid Alert/Non-urgent Message
- Reference:
- From:
- To:
- Date:

2. Veterinary Medicinal Product

- Brandname(s):
- Active substance(s): (INN, DCI)
 - κ - Centrally Authorised Product,
 - τ - Nationally Authorised Product,
 - > - Mutual Recognition Product,
 - × - Product which has been subject to a referral process
- Pharmaceutical form and dosage (if appropriate):
- Marketing Authorisation Holder(s)
- Manufacturer (if essential)

3. Reason for Alert

- Source of information: Spontaneous reports/Post-Authorisation Study/Clinical Trial/Pre-clinical Study, others
- summarised evidence relevant to alert

4. Actions

- Action(s) proposed
- Action(s) taken (steps taken to collect more information at a national level and temporary steps taken to limit risks)

5. Information exchange

- Information required

Annex II

Guideline on Pharmacovigilance Assessment Reports

Format and content

I. Introduction

This section should clarify why the assessment has been undertaken.

II. Assessment of risks

This section will be specifically devoted to the safety concern under evaluation. It should encompass all relevant sources of information, including spontaneous reports, including death, published literature, studies (pre-marketing clinical trials, post-marketing studies, epidemiological studies and intensive monitoring data):

- a) characterise the problem (nature, severity, outcome);
- b) assess causal association;
- c) estimate frequency and comparative frequency, where possible;
- d) provide evidence of risk factors

III. Assessment of benefits

It should take into account the following, where known:

- a) the nature of the diseases/signs for which the veterinary medicinal product is indicated (e.g. fatal, life-threatening, economic importance.)
- b) absolute efficacy, as judged by controlled clinical trials
- c) relative efficacy, as judged by studies comparing efficacy with that of appropriate alternative treatment(s)
- d) the characteristics of the population exposed to the medicine

IV. Overall risk-benefit assessment

This section includes:

- a) an overall benefit/risk analysis in the context of the safety problem under assessment and relevant comparative safety with other drugs in the same class or for the same therapeutic indication;
- b) discussion of the optional actions for improving the risk-benefit ratio
- c) proposed actions for responding to the safety issue.

Annex III

**TEMPLATE FOR
FINAL ASSESSMENT REPORT FOLLOWING THE RAPID ALERT**

OF

< ACTIVE INGREDIENT >

<The INN name should be used>

Status: < for INFORMATION >

Reference No < >

From: <Member State>

Date: <dd-mm-yy>

Signature: <.....>

Name: <.....>

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PRODUCT PROFILE AND ABSTRACT OF THE PROCEDURE

BACKGROUND INFORMATION

Starting Point

Referral to national advisory board

The proceedings of the national inquiries

Alerting the Member States

Involvement of the CVMP Pharmacovigilance Working Party

SCIENTIFIC DISCUSSION

Overview of the safety concerns

Overview of benefits

Overall risk - benefit assessment

PROPOSED ACTIONS / ACTIONS TAKEN

National variation of marketing authorisation

National suspension of the marketing authorisation

National withdrawal of the marketing authorisation

Referral to CVMP

ANNEXES

ABSTRACT OF THE ALERT PROCEDURE AND PRODUCT PROFILE
(on one page)

Alerting Member State

Problem/Subject

Veterinary Medicinal Product

- INN name
- Brand name(s)
- Company
- Strength(s)
- Pharmaceutical form(s)
- Route of administration
- Therapeutic Classification (ATC-Vet code)
- Marketing Authorisation Holder

Animals Involved

Indications

Reason for Alert

Proposed action or action taken

BACKGROUND INFORMATION ON THE PROCEDURE

Starting Point

- When
- By whom
- The concern
- The veterinary medicinal product concerned
- The source of the concern
(e.g. case reports from spontaneous reporting, epidemiological study)

Referral to the National Advisory Board

- When
- Which matter
- National procedure for actions to be taken

The proceedings of the National inquires

- When
- On which problem
- On which substance
- Involvement of the Marketing Authorisation Holders
 - ⇒ Time frame
 - ⇒ Explanations of the MAH(s) in writing/orally

Alerting the Member States

- When, by (e.g. Fax, e-mail)
- On which problem
- On which INN-name
- Call for (e.g.)
 - ⇒ case reports
 - ⇒ details of legal status in the Member State

⇒ information on supply and use

- Answers received from

Involvement of the Veterinary Pharmacovigilance Working Party

- The subject was

⇒ presented by, when

⇒ discussed on, when

- Additional explanations of the MAH(s) were given

⇒ when

⇒ in writing (expert report)

⇒ orally

- Assessment reports were prepared

⇒ by , when

⇒ reviewed, updated, finalised

- A report of the Veterinary Pharmacovigilance Working Party was given

⇒ when

⇒ to (e.g. the CVMP, the MAH, others)

SCIENTIFIC DISCUSSION

- Overview of the safety concerns

⇒ Adverse Reactions

⇒ Risk of correct treatment (e.g. defined populations at risk)

⇒ Risk of inappropriate treatment (if applicable)

- Overall risk - benefit assessment

⇒ of the veterinary medicinal product under consideration

⇒ place on the market

⇒ compared to alternative treatment(s)

PROPOSED ACTIONS / ACTIONS TAKEN

- Variation of the marketing authorisation
 - ⇒ Proposed conditions of supply and use
 - ⇒ Proposed warnings to animal health professionals and/or animal owners
 - ⇒ Proposed changes of the SPC or parts of it
 - ⇒ Provision of further evaluation for the MAH(s)
- Suspension of the marketing authorisation
 - ⇒ from, to
 - ⇒ with obligation to fulfil in between
- Withdrawal of the marketing authorisation
 - ⇒ in force from
 - ⇒ recall of products on the market is included and monitoring of the recall process
- Referral to CVMP
 - ⇒ Community interest involved

ANNEXES

(Annexes if appropriate,)

Template A

Logo and name of the Competent Authority of the Member State/Agency

<RAPID ALERT / NON-URGENT INFORMATION> IN VETERINARY PHARMACOVIGILANCE		
Reference:	N° of attachments:	Date:
FROM:		
TO: (ALL) MEMBER STATES EFTA countries concerned Agency EUROPEAN COMMISSION CHAIR-CVMP RAPPORTEUR (if applicable) RMS (if applicable)		

SUBJECT:

Please fill in the appropriate fields

Brandname(s): <select K | t | > | x>

International Non-proprietary Name (INN, DCI) or Class: <select K | t | > | x>

Strength(s):

Pharmaceutical Form(s) and Dosage(s):

Route of Administration(s):

Therapeutic Classification (ATC code):

Marketing Authorisation Holder:

Indication(s):

REASONS FOR <ALERT / NON-URGENT INFORMATION>:

(Relevant Summarised Evidence)

(Text)

Source of Information:

Please select:

Spontaneous Reports

Post Marketing Study

Clinical Trial

Preclinical Study

Other (please indicate)

PROPOSED ACTION AND ACTION TAKEN:

(Text)

INFORMATION REQUESTED:

(Text)

ADDITIONAL INFORMATION:

(Text)

Please respond by --/--/--

Name of person responsible for sending message:

Template B

Logo and name of the Competent Authority of the Member State/Agency

ANSWER TO <RAPID ALERT / NON-URGENT INFORMATION> IN VETERINARY PHARMACOVIGILANCE

Reference:

N° of attachments:

Date:

FROM:

IN ANSWER TO THE ORIGINAL MESSAGE FROM <MEMBER STATE> DATED --/--/--

TO: (ALL) MEMBER STATES
EFTA Countries concerned
Agency
EUROPEAN COMMISSION
CHAIR-CVMP
RAPPORTEUR (if applicable)
RMS (if applicable)

Respond requested by originator for --/--/--

SUBJECT:

Please fill in the appropriate fields

Brandname(s): <select K | t | > | x >

International Non-proprietary Name (INN) or Class: <select K | t | > | x >

Strength(s):

Pharmaceutical Form(s) and Dosage(s):

Route(s) of Administration:

Therapeutic Classification (ATC code):

Marketing Authorisation Holder:

Indication(s):

**ANSWER TO <RAPID ALERT / NON-URGENT
INFORMATION>:**

(Text)

PROPOSED ACTION AND ACTION TAKEN:

(Text)

ADDITIONAL INFORMATION:

(Text)

Name of person responsible for sending message:

Section 3: Guidelines for Post-Marketing Surveillance of Veterinary Medicinal Products

1. Objectives of these guidelines

Surveillance of marketed veterinary medicinal products is a shared responsibility of the Competent Authorities and Marketing Authorisation Holders (MAH).

Before granting of a marketing authorisation for a veterinary medicinal product, aspects of quality, efficacy and safety of the new veterinary medicinal product are assessed by experts of the regulatory authority with the aim to guarantee a maximum of safety.

However in some cases this aim can not be achieved by a scientific evaluation before granting the marketing authorisation. It may be necessary to undertake a continuous surveillance of the veterinary medicinal product under field conditions for a defined period of time after the marketing authorisation is granted.

Although with veterinary medicines there is a well recognised advantage over human medicines, in that the conduct of pharmaco-toxicological trials can be conducted in target animal species, not all potential adverse effects will be expressed in these trials with a limited number of animals. Many adverse reactions can be seen only after the use of the veterinary medicinal product in clinical practice in a large population of animals. Sensitive subpopulations such as young animals or specific sensitivities of animal species and breeds can only be discovered by use of the veterinary medicinal product on a large scale.

Post-marketing surveillance of veterinary medicinal product therefore plays an important role to discover undesirable effects that might present a risk for animal health, public health or environment. Post-marketing surveillance studies provide additional information on the benefits and risks of a veterinary medicinal product, resulting in possible safety hazards being identified which impact on, or may influence the overall benefit/risk ratio of the veterinary medicinal product. As a result the competent authority may request, or the MAH may propose appropriate measures of risk prevention or propose studies to further investigate the hazard and frequency of its occurrence. Such studies should comply with the guidance in this chapter.

If the risk is not acceptable compared to the therapeutic value of a drug, regulatory measures might be initiated to keep the benefit risk balance on a positive scale.

Post-marketing surveillance studies should compliment spontaneous adverse reaction reporting systems, which are very important in the detection of background signals, which might indicate a problem. However spontaneous reporting systems do not provide a quantitative risk assessment i.e. give the incidence of an adverse reaction in a population. Therefore it is difficult to estimate the relevance of a risk described in single case reports, without knowing the number of exposed and treated animals within a given time period. Post-marketing surveillance studies can provide a denominator and give the answer to specific questions, which have been generated by signals from the spontaneous adverse reaction reporting system.

A commitment to post-marketing surveillance studies (PMS) may be required at the time of marketing authorisation. In this case the study should be carried out on the basis of information of the Summary of Product Characteristics and in accordance with *Good Veterinary Clinical Practice* (ref.: Vol. 7 of *The Rules Governing Veterinary Medicinal Products in the European Union*).

The basic types of questions to be addressed in PMS studies are:

- long term effects-that manifest themselves only after long periods of use, or after long periods of latency
- low frequency effects that can only be detected in large populations

- efficacy in customary practice
- modifiers of efficacy: concurrent products, disease severity, husbandry conditions, feed
- increase in frequency or severity of known adverse reactions

In veterinary pharmacovigilance as the scope is set wider than for human medicinal products, see Part II, chapter 1, for guidance on *Pharmacovigilance of Veterinary Medicinal Products* monitoring of surveillance of ecotoxicity might also be an objective of post-marketing surveillance.

In veterinary pharmacovigilance until now, there is little experience on conducting post-marketing surveillance studies. Although the methodology must be sometimes adapted to quite specific aspects of the veterinary field, profit can be gained from the experience in human medicine post-marketing surveillance. As pharmacoepidemiological science and methods are basically the same regardless of the species concerned, similar procedures whenever possible should be used and adapted to the veterinary sector.

1.1 Scope of the guidance in this chapter

The guidance in this chapter applies to the conduct of studies, which embraces the safety of marketed veterinary medicinal products. These could be

- i) post-authorisation safety studies sponsored by the company
- ii) or post-authorisation studies not sponsored by the company

It includes studies where the drug is provided by the sponsoring company and studies where it is prescribed and used in the normal conditions of clinical veterinary practice.

It provides a framework whereby a variety of data collection methods can be used to evaluate the safety of marketed veterinary medicinal products. Though the study design used must be adopted on a case by case basis for particular products and hazards the guideline defines the essential principles to be applied in a variety of situations.

As the study methods in this field continue to develop, there will be a need to regularly review the guidance in this section to ensure that it reflects advances made in the assessment of product safety.

1.2 Post-marketing surveillance studies (PMS)

Post-marketing surveillance study means a pharmacoepidemiological study or clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard to an authorised veterinary medicinal product.

The guidance in this section relates principally to those studies where there is a known safety issue under investigation and/or when the number of animals to be included in the study will add significantly to the existing safety data already provided for the product(s).

If a study, which is not conducted for the purpose of evaluating safety, unexpectedly, identifies a hazard, then the study would be included in the measures laid down in the guidance in this section.

Clinical trials for new indications, new methods of administration or new combinations, are not covered by the guidance in this section.

In cases of doubt as to whether or not a study comes under the scope of the guidance in this section the person responsible for the study should discuss the intended protocol with the relevant regulatory authority of the member state (s) in which the study is to be conducted.

1.3 Extent and objectives of post-marketing surveillance studies

PMS may be conducted for the purpose of identifying previously unrecognised safety issues (hypothesis- generation), investigating possible hazards (hypothesis testing in order to substantiate a causal association) or confirming the expected safety profile of a veterinary medicinal product under marketed conditions. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Objectives may be

- i) to measure the incidence of an adverse reaction in animals treated with the suspected drug
- ii) to compare the incidence of an adverse reaction in animals treated and not treated with the drug
- iii) to identify the risk factors associated with the development of an adverse reaction in animals treated with the suspected drug, such as concurrent drugs, disease severity, husbandry conditions, breeds, age, feed, etc
- iv) to identify risk factors responsible for an increased frequency or severity
- v) to further clarify biological effects of adverse reactions due to a suspected drug

The design to be used will depend on the objectives of the study, which must be defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods.

1.4 Design of studies

1.4.1 Observational cohort studies

Cohort studies have the advantage to provide information about the incidence of an event in a primarily unaffected population group. It is possible to test a hypothesis defined prior to the start of the study, which could take a prospective or retrospective approach.

The results allow an assessment of risk (relative, absolute and population attributable risk).

The disadvantages could be that they are mainly useful for frequent events, they necessitate large population samples, they are time consuming and costly.

- a) The animal population studied should be as representative as possible of the general population of animals normally treated and be unselected unless specifically targeted by the objectives of the study. Exclusion criteria should be limited to the contra-indications and special warnings stated in the SPC. In prospective studies the veterinarians involved in the study should be provided with the SPC for all products to be used. Where the product is used outside the indications of the SPC at the discretion of the prescribing veterinarian, such animals should be included in the analysis of the study findings.
- b) Observational cohort studies should normally include appropriate control group(s). These groups will usually include animals with the disease/indication(s) relevant to the primary study product and such animals will usually be treated with alternative therapies.
- c) The protocol should stipulate the minimum and maximum number of animals in each trial supervised by each veterinarian.

1.4.2 Case control studies

This study type allows hypothesis testing in a relatively short time at low cost. The approach to the research question can be concurrent or historic. It provides information for rare events and the relative risk can be estimated by calculating the odds ratio.

The disadvantages are that this study type is susceptible to bias and confounding factors and it allows no incidence estimate, nor a calculation of the absolute risk. The selection of proper controls is particularly important for this study type.

Case control studies are usually conducted retrospectively. Comparison is made between the product exposure of cases with the disease/event of interest and appropriate controls without the event. The study design should account for known sources of bias and confounding factors.

1.4.3 Group surveillance

The purpose of group surveillance is to study groups of animals where problems may arise which could be product-related and to ascertain product exposure. Companies who sponsor such studies should liaise particularly closely with the relevant regulatory authority in order to determine the most appropriate arrangements for the reporting of cases. Regulatory agencies may require such surveillance programmes to acquire information on emerging trends in large populations in relation to safety and/or efficacy.

1.4.4 Clinical trials

Specific clinical trials are sometimes necessary to clarify the mechanisms of adverse reactions and to identify the means of prevention. Large clinical trials may also be useful in the investigation of post-marketing safety issues and these may involve random allocation to treatment. Exclusion criteria should normally be limited to the contra-indications in the SPC unless they are closely related to the particular objectives in the study. Clinical trials should also adhere to Good Clinical Practice.

1.5 Conduct of studies

Responsibility for the conduct of the study shall be vested in the sponsor.

It shall be supervised by designated monitor(s) sited within the EU, and whose names shall be recorded in the study documents. Consideration should be given to the appointment of an independent advisory group to monitor the data and oversee the study.

1.6 Liaison with competent authorities

Companies or other institutions such as universities, proposing to perform a post-authorisation safety study are advised to discuss the draft protocol at an early stage with the relevant regulatory authority. Particular consideration should be given to specific safety issues, which may require investigation. National legislative requirements or guidelines should be taken into account where these exist.

Before the study commences a protocol must be finalised which explains the aims and objectives of the study, the methods to be used (including statistical analysis) and the record keeping which is to be maintained. The company should submit the protocol plus any proposed communications to veterinarians participating in the study to the relevant regulatory authorities at least one month before the planned start of the study. The authorities may comment as necessary. The responsibility for the conduct of the study will, however rest with the sponsoring pharmaceutical company.

The company should inform the relevant authorities when the study has commenced and will normally provide a brief report on its progress every six months, or as requested by the authorities.

The usual reporting requirements for reporting of suspected adverse reactions must be fulfilled. Companies should ensure that they are notified of serious suspected adverse reactions and should report these to the relevant regulatory authorities within 15 days of receipt. All non-serious events should not be reported individually, but they should be summarised in the final report.

A final report on the study should be sent to the relevant regulatory authorities within 3 months of follow-up being completed. Ideally this should be a full report but a brief preliminary report within 3 months followed by a full report within 6 months of completion of the study would normally be acceptable.

In the case of products authorised through the centralised procedure, progress reports and final reports should also be sent to the Agency.

Companies should follow the Good Veterinary Clinical Practice guidelines on the content of the protocols, and final reports. For progress reports, an example is given here:

Suggested content of progress report

- i) Tabulation of number of patient animals identified as suitable for the study, *animals* entered and followed up
- ii) Estimate of overall exposure to study product(s) in patient-years or months or days
- iii) Status of all patients who have completed the study e.g. on/off treatment, died, lost to follow up
- iv) Tabulation of the reasons for stopping treatment during the study
- v) Individual listing of causes for each death and animals needing care in specialist clinics
- vi) Table of all serious adverse events (numerical form plus a line-listing)

N.B. If there are multiple study products, data should be reported for each product separately.

Generally only the data listed above should be included. Other information should not be included without prior discussion with the regulatory authorities. After review of the report regulatory authorities may request additional information.

They may require adaptation to suit the needs of individual studies.

1.6.1 Promotion of veterinary medicinal products

Post-marketing surveillance studies should not be conducted for the purposes of promoting the use of veterinary medicinal products. Marketing Authorisation Holders representatives should not be involved in studies in such a way that it could be seen as a promotional exercise.

1.6.2 Procedure for complaints

All post-marketing safety studies should be referred to the relevant regulatory authorities, or, if appropriate, to other bodies within the Member States which are deemed to have the matter within their remit.

Section 4 : Terminology

- a) Adverse Reaction means a reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function
- b) Human adverse reaction means a reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine;
- c) Serious adverse reaction means an adverse reaction which results in death ,is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated;
- d) Unexpected adverse reaction means an adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of the Product Characteristics;
- e) Serious unexpected adverse reaction means an adverse reaction which is both serious and unexpected.
- f) Post marketing surveillance studies means pharmacoepidemiological study or clinical trial carried out in accordance with the Marketing Authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised veterinary medicinal product;
- g) Off –label use means the use of a veterinary medicinal product that is not in accordance with the Summary of the Product Characteristics, including the misuse and serious abuse of the product;
- h) Periodic safety update reports means the periodical reports containing the records referred to in Article 75
- i) Misuse: use of a veterinary medicinal product in a way which is not recommended in the summary of product characteristics, with the exception of those cases referred to in Article 10 of Directive 2001/82/EC .
- j) Abuse: persistent or sporadic, intentional excessive use or administration of a veterinary medicinal product inconsistent with or unrelated to the recommendations of the summary of the product characteristics.

These definitions are firstly provided in Directive 2001/82/EC, Title I Article 1.

**PART III - EU ELECTRONIC EXCHANGE OF
PHARMACOVIGILANCE INFORMATION**

Background

Taking into account the new developments related to the efficient electronic exchange of pharmacovigilance information based on the activities of ICH and V-ICH, this document provides a reference for the preparation and electronic submission of Individual Case Safety Reports including the minimum requirements for Periodic Safety Update Reports related to Human and Veterinary Medicinal Products authorised within the European Union.

1. Introduction

The rapid and secure exchange of pharmacovigilance information is of utmost importance to guarantee the protection of human and animal health within the European Union (EU).

The agreement on the specifications for the electronic exchange of Individual Case Safety Reports (ICSRs) and Periodic Safety Update Reports (PSURs) in line with the recommendations of the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (referred to as ICH) and the recommendations, which will emerge in the framework of the International cooperation on Harmonisation of Technical Requirements for registration of veterinary products (referred to as VICH) will change the current way of conducting pharmacovigilance in the EU radically.

To minimise preparation time and costs of processing submitted data and to achieve uniformity and a high quality of submission content and format between all involved partners it is the objective to move away from a paper based reporting system towards electronic transmission of pharmacovigilance information.

An important evolution in the concept of pharmacovigilance and in the requirements for exchange of information in the Community has been also achieved by the new system for marketing authorisation and supervision of medicinal products for human and veterinary use based on Council Regulation (EEC) No. 2309/93.

According to Article 51, paragraph c, the Agency is responsible for the co-ordination of the supervision of medicinal products, which have been authorised within the Community. Furthermore, the Agency is responsible for the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluating and making available information on adverse reactions to the medicinal products in question through a pharmacovigilance database.

Article 24 and 46 of Council Regulation (EEC) 2309/93 of July 1993 state that the Agency in consultation with Member States and the European Commission (EC), shall set up a data-processing network for the rapid transmission of data between the competent Community authorities in the event of an alert, relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding human or veterinary medicinal products marketed in the Community.

The exchange and management of ICSRs and PSURs are based on the obligations and activities placed, through legislation, on a number of parties, i.e. the competent Community authorities Member States, the Agency and the Marketing Authorisation Holders (MAHs).

To support the fulfilment of these obligations, the EC, in January 1996, launched a project called 'EudraVigilance and EudraNet' with two main objectives:

- The deployment and operation of EudraNet, a telematic network in the pharmaceutical field between the European Commission, the Agency and the National competent authorities to allow the fast and secure exchange of information between those parties,

- The development and operation of EudraVigilance, an EU Pharmacovigilance system, in full compliance with the definition of the data and message models concerning pharmacovigilance information about human and veterinary medicinal products as defined in the relevant ICH and Veterinary guidelines designed to
 - ⇒ support the electronic exchange, the management and the scientific evaluation of ICSRs and PSURs in line with the international harmonisation agreements,
 - ⇒ provide a centralised database containing high quality data on adverse reactions occurring within and outside the EU, supporting the competent authorities in Member States and the Agency, responsible jointly for the surveillance of the safety and efficacy of medicinal products for human use and veterinary medicinal products, in their pharmacovigilance activities.

In order to achieve a fast and efficient integration of the substantial changes in how pharmacovigilance information is exchanged and managed it is necessary that the competent authorities in Member States, the Agency and MAHs work together in a collaborative and co-operative manner. This co-operation has to ensure that the electronic transmission of ICSRs and later of PSURs when the specifications have been finalised, are performed in a fast and quality controlled manner.

Further, it is necessary to put procedures in place to avoid duplication of data, maintain confidentiality and to ensure the quality and compatibility of the established pharmacovigilance systems. EudraVigilance and the pharmacovigilance systems established by the competent authorities in Member States will be an important contribution to the utilisation of efficient signal generation, scientific analysis and risk assessment on the provided data.

The objective of this document is to provide a reference for the preparation and electronic submission of ICSRs including the minimum requirements for PSURs related to human and veterinary medicinal products authorised within the European Union that will support the achievements of the goals as set out.

2. Reference Documents

The electronic transmission and management of ICSRs and PSURs will be carried out according to the following guidelines and specifications:

2.1 Medicinal Products for Human Use

- The **ICH E2A** guideline '*Clinical Data Management: Definition and the Standards for Expedited Reporting*' EUDRALEX Volume 3C, which presents the standard definitions and terminology for key aspects of clinical safety reporting and provides guidance on the appropriate mechanism for handling expedited reporting in the investigational phase.
- The **ICH E2B** guideline '*Data Elements for the Electronic Transmission of Individual Case Safety Reports*' Part IV, Chapter 3 which extends the above guideline to standardise the data elements for the transmission of all types of ICSRs, regardless of their source and destination.
- The **ICH M2** '**Specification of the message for the Electronic Transmission of Individual Case Safety Reports**'.
- The **ICH E 2C** '*Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*' reproduced here as Part IV, chapter 2, which provides guidance on the format and content of safety updates, which need to be provided to regulatory

authorities, at defined intervals, after the medicinal products have been authorised. The guideline is intended to ensure that the world wide safety experience is provided to authorities at defined time intervals after authorisation with maximum efficiency and avoiding duplicating effort.

- The Medical Dictionary for Regulatory Activities (**MedDRA**). The new terminology is designed to support the classification, retrieval, presentation and communication of medical information throughout the medicinal product regulatory cycle.(see Chapter 3.2, Part I)
- **The Standard Terms on Pharmaceutical Dosage Forms**

For the description of the pharmaceutical dosage forms the ‘Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers’ as published by the Council of Europe are applicable in the latest version.

2.2 Veterinary Medicinal Products

- The **VEDDRA List** of Clinical Terms/Terminology for Animal Suspected Adverse Reactions to Veterinary Medicinal Products designed to support the classification, retrieval, presentation and communication of adverse reactions in animals related to the administration of veterinary medicinal products.

Implementation: finally adopted by the Veterinary Pharmacovigilance Working Party (PhVWP) on behalf of the CVMP, 4 September 2002, (EMEA/CVMP/413/99-Final)

- The **VEDDRA Species List** designed to support the classification, retrieval, presentation and communication of animal species related to the class, the animal role, the production type and the sex.

Implementation: under revision - adopted by the Veterinary Pharmacovigilance Working Party (PhVWP) on behalf of the CVMP, 16 April 1999, (EMEA/CVMP/PhvWP/024/99)

- Pharmacovigilance of veterinary medicinal products: management of Adverse Reactions Reports
- *Implementation: to be adopted by the CVMP following sign off of step 5 at VICH* The Medical Terminology **MedDRA** may support the classification, retrieval, presentation and communication of adverse reactions in humans related to the use of veterinary medicinal products (for details please refer to Medicinal Products for Human Use).

- **The Standard Terms on Pharmaceutical Dosage Forms**

For the description of the pharmaceutical dosage forms the ‘Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers’ as published by the Council of Europe are applicable in the latest version.

3. Message Format

3.1 Medicinal Products for Human Use

Safety Messages and Safety Reports related to medicinal products for human use will be structured according to the ICH E2B Guideline and the ICH M2 Message Specification for the Electronic Transmission of Individual Case Safety Reports.

3.2 Veterinary Medicinal Products

The Safety Messages and the Safety Reports related to veterinary medicinal products will respond to the guidelines of VICH and the CVMP when available.

4. Terms and Definitions

4.1 General Terms

Individual Case:	An individual case is the information provided to describe suspected adverse drug reaction(s) related to the administration of one or more medicinal products to an individual patient or to one or more animal(s).
Case Safety Report:	A case safety report is a document providing the most complete information related to an individual case available at a certain point of time.
Reporter:	The reporter is the primary source of the information, i.e. a person who initially reports the facts. This should be distinguished from the sender of the message, though the reporter could also be a sender .
Sender:	The sender is the person or entity creating the message for transmission. Although the reporter and the sender may be the same person, the function of the sender should not be confused with that of the reporter.
Receiver:	The receiver is the intended recipient of the transmission.
Safety Message:	The safety message is the information provided for one/more case safety reports contained in one safety file exchanged between one sender and one receiver in one transaction.
Acknowledgement Message:	The acknowledgement message is the information provided to acknowledge one safety message and the safety report(s) contained in the safety file of this message, exchanged between one sender and one receiver in one transaction.
Safety Message File:	The safety message file is the electronic file transmitted in one transaction between one sender and one receiver containing one safety message.
Transaction:	A transaction is a set of actions encompassing the electronic transmission of a message.

4.2 Identification

Sender Identifier:	The attribute 'Sender identifier' (A.3.1.2, ICH E2B) identifies the sender e.g. company name or regulatory authority name and is mandatory for each report.
Message Sender Identifier:	The attribute 'Message sender identifier' (M.1.5, ICH M2) identifies the sender of the message and should in principal coincide with the organisation specified as the 'Sender identifier' (A.3.1.2, ICH E2B).
Message Receiver Identifier:	The attribute 'Message receiver identifier' (M.1.6, ICH M2) identifies the receiver of the ICSR reports, e.g. company name or regulatory name and coincides with the organisation specified as receiver at report level (A.3.2.2a, ICH E2B).
Recent Info Date:	The attribute 'Date of receipt of the most recent information for this report' (A.1.7b, ICH E2B) can be defined as the date when the most recent information for an individual case report currently being transmitted was received by the sender.
Sender's case safety report unique identifier:	This identifier should remain constant in the subsequent transmission of the case by the same sender. Retransmitter should replace this value with their own unque identifier.
Worldwide unique Case Identification:	<p>The case identification (CaseID) is the unique identifier defined at the moment of the creation of the case (in a database or on paper) by an authorised source and is indicated in the A.1.10 block of the report.</p> <p>According to the definition of ICH E2B three identification numbers are specified. One and only one of the following fields must be populated:</p> <p>Regulatory authority's case report number: identifier given by a national regulatory authority (A.1.10.1, ICH E2B),</p> <p>Other sender's case report number: identifier used by senders who are not representing either a pharmaceutical company or a regulatory authority (A.1.10.2, ICH E2B).</p> <p>As indicated in the ICH M2 guideline, that field value should remain unchanged all through the life cycle of the report, no case should ever have more than one of these items completed.</p> <p>The value for these fields must be a concatenation of Country code-, organisation code-, report number, relative to the organisation that has created the case report separated by hyphens.</p>
Safety Report Identification:	A report is identified by the report identification (ReportID). The ReportID identifies the document describing a case with the most recent and most complete information available at a point in time.
Report Sequence:	The report sequence (Report SQ) is the sequential position of one safety report in one message.

Local Report ID:	On the receiver side, a local report ID may be assigned to each incoming report.
Message Identification:	The Message(file)ID is defined at the moment of the creation of the file.
Local Message ID:	On the receiver side, a local message ID may be assigned to each incoming message.
Transaction ID:	The transaction ID should be created at the transaction level, eventually by the EDI server. It is common to all the messages in the transaction and should contain complete information on the sender/receiver, the time the information was sent/received, if the transaction was successful/unsuccessful. It is included in the EDI Interchange header.

For further definitions please refer to the ICH E2B guideline *Data Elements for the Transmission of Individual Case Safety Reports*, Part IV, chapter 3, the ICH M2 guideline *Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR Version 2.0)* and to Part II, chapter 1 *Pharmacovigilance for Veterinary Medicinal Products*.

4.3 Mandatory Information

It is recognised that it is often difficult to obtain all details on a specific case. However, the complete information related to an individual case, that is available to the sender, has to be reported in accordance with the legal requirements as set out in the Community legislation.

This may also include causality assessment if requested by competent authorities.

In addition, whenever more recent information on an individual case is submitted, the complete (entire) information on the case has to be provided and not only partial information e.g. changes or updates.

This does not only apply to the submission of follow-up information but also if an ICSR is highlighted for nullification. For those ICSRs that are highlighted for nullification ('Report nullification', A.1.13 ICH E2B, set to 'yes') the reasons for nullification must be indicated in detail.

From a procedural point of view the following should be considered:

- *Sender Identifier (A.3.1.2, ICH E2B)*

The 'Sender identifier' and the 'Message sender identifier' are unique for each sender organisation and defined as indicated in the interchange agreement with the Agency and/or National competent authorities.

Sender identifier (A.3.1.2, ICH E2B) and the message sender identifier (M 1.5. ICH M2) must, from the receiver's point of view, be identical.

- *Date of receipt of the most recent information for this report (A.1.7b, ICH E2B)*

To allow the check on the recent info date from a technical point of view the sender has to comply with the following rules:

In the initial report (describing the case for the first time) the field 'date of receipt of most recent information for this report' must be filled in and should contain the same information as the field 'date report was first received from source'.

If more recent information is submitted on the case at a later time the 'Date of receipt of most recent information for this report' has to include the date on which the sender actually received the most recent information.

- *Worldwide unique Case Identification Number (A.1.10.1, A.1.10.2., ICH E2B)*

As indicated in the ICH M2 guideline the contents of the A.1.10 elements:

National regulatory authority's case report number (A.1.10.1, ICH E2B)

Other sender's case report number (section A.1.10.2, ICH E2B)

should be populated only once worldwide and should remain unchanged for any transmission subsequent to the original transmission.

4.3.1 Human Medicinal Products

Based on the definitions as described in the ICH E2B guideline, *See Part IV, chapter 3*, the fields as specified in the table below are regarded as the minimum mandatory information to be provided for human safety reports.

Within the fields of the six sections described in the table below, mandatory (M) indicates that information related to this field must be provided in any case. Where a field is specified as mandatory optional (MO), it is mandatory to provide at least one or if possible more fields within the relevant section. Reports that do not contain this minimum information are not considered as valid reports.

Section-Field Title	Mandatory M Mandatory-Optional MO
Section: Safety Report Identification	
A. 1. 6b- Date report was first received from source	M
A.1.7b - Recent Info Date (Report)	M
A.1.10.1 - National regulatory authority's case report number	MO
A.1.10.2 – Company's case report number	MO
A.1.10.3 - Other sender's case report number	MO
Section: Primary Source	
A.2.1.1.d – Reporter family name	MO
A.2.1.2.a – Reporter organisation	MO
A.2.1.2.f – Reporter postcode	MO
A.2.1.3 – Reporter country code	MO
A.2.1.4 – Reporter qualification	MO
A.2.2 – Literature reference(s)	MO
A.2.3.1 - Study name	MO
Section: Sender	
A.3.1.2 – Sender Identifier (=sender organisation)	M
Section: Patient	
B.1.1 – Patient initials	MO
B.1.1.1 a – GP medical record number	MO
B.1.1.1 b – Specialist record number	MO
B.1.1.1 c – Hospital record number	MO
B.1.1.1 d – Investigation number	MO
B.1.2.1 b – Date of Birth	MO
B.1.2.2 a – Age value at time of onset reaction/event plus	MO
B.1.2.2 b – Age unit	MO
B.1.2.3 – Patient age group	MO
B.1.5 – Sex	MO

Section: Reaction	
B.2.i.2 – Reaction term using MedDRA LLT codes or terms in English	M
Section: Drug	
B.4.k.2.1 – Proprietary medicinal product name	MO
B.4.k.2.2 – Active drug substance names in English	MO

4.3.2 Veterinary Medicinal Products

Based on the definitions in Part II, chapter 1 *Pharmacovigilance for Veterinary Medicinal Products* the fields as specified in the table below are regarded as the minimum information mandatory for veterinary adverse reaction reports.

Within the fields of the eight sections described in the table below, mandatory (M) indicates that information related to this field must be provided in any case. Where a field is specified as mandatory optional (MO), it is mandatory to provide at least one or if possible more fields within the relevant section. Depending if the report describes an adversereaction that occurred in an animal or in a human either the relevant sections ‘Animal’ and ‘Animal Adverse Reaction’ or ‘Human’ and ‘Human Adverse Reaction’ need to be completed. Reports that do not contain the required minimum information are not considered as valid reports.

Section-Field Title	Mandatory M Mandatory-Optional MO
Section: Safety Report Identification	
Date report was first received from source	M
Recent Info Date (Report)	M
National regulatory authority’s case report number	MO
Company’s case report number	MO
Other sender’s case report number	MO
Section: Primary Source	
Reporter family name	MO
Reporter organisation	MO
Reporter post code	MO
Reporter country	MO
Reporter qualification/occupation (e.g. physician, vet practitioner, pharmacist, animal owner, other)	MO
Section: Sender/Final Receiver	
Sender organisation	M
Sender type (e.g. Pharmaceutical Company, Regulatory Authority)	M
Section: Animal	MO
Animal Species	M
Animal Sex	MO
Animal Age	MO
Number of Animals treated	MO
Section: Animal Adverse Reaction	MO
Reaction term using the LLT of the VEDDRA List of Clinical Terms (codes or terms in English)	M
Section: Human	MO
Patient identifier (Surname and first name of the patient if available and acceptable under national law, or some other identifier e.g. initials of surname and all forenames)	MO
Gender (Sex of the patient)	MO
Age (Patient age at time of onset of reaction)	MO

Section: Human Adverse Reaction	
Reaction term (if appropriate ,description of the reaction using MedDRA LLT level codes or the term in English)	M
Medicinal Product	
Medicinal product name/brand name	MO
Active substance(s) List of ingredient names (composition) (INN) in English	MO

4.4 Community Languages

The handling of uncoded information (free text) in different languages is an important issue for the management and the usability of pharmacovigilance information across the EU.

It is therefore agreed that the information in the narrative fields (uncoded information) of safety reports related to adverse reactions

- Occurring within the Community may be provided in one of the official Community languages, whereby English would be the preferred one;²⁰
- Occurring in the territory of a third country will be provided in English.

5. Standard Terminology

ICSRs and PSURs submitted electronically will be compliant with the following codification and terminology. Additional information will be found in the ICH E2B (*Part IV, chapter 3*) and M2 guidelines.

5.1 Medicinal Products for Human Use

- **Medicinal Product terms**

The data items:

Proprietary Medicinal Product Name	(B.4.k.2.1 ICH E2B/M2)
Active Drug Substance Names	(B.4.k.2.2 ICH E2B/M2)

in the Safety Report message will be provided for centrally authorised medicinal products in compliance with the Community Register of Medicinal Products for Human Use published in accordance with Article 12 of Council Regulation (EEC) N°2309/93; medicinal product names and active drug substance names which are not part of the Community Register will be submitted in compliance with the WHO Drug Dictionary.

- **Reaction terms**

The data items:

Reaction term	(B.2.i.1.b ICH E2B/M2)
Disease/Surgical procedure	(B.1. 7.1a.2 ICH E2B/M2)
Reported Cause of Death	(B.1.9.2.b ICH E2B/M2)
Autopsy-determined cause(s) of death	(B1.9.4b ICH E2B/M2)

²⁰ If the information in the narrative fields is provided in a different Community language besides English, it is recommended to submit a summary of the data in English.

Relevant medical history and concurrent conditions of parent-Disease/Surgical procedure	(B.1.10.7.1a.2 ICH E2B/M2)
Structured Information (results from tests and procedures) relevant to the investigation of the patient	(B.3.1c ICH E2B/M2) (B.3.1d ICH E2B/M2)
Indication for use in the case	(B.4.k.11 ICH E2B/M2)
Which reaction recurred (re-challenge)	(B.4.k.17.2 ICH E2B/M2)
Sender's diagnosis/syndrome and/or reclassification of reaction	(B.5.3 ICH E2B/M2)

will be provided in compliance with the LLT numeric code or English term of the MedDRA medical dictionary.

- **Routes of administration**

The data items:

Route of administration	(B.4.k.8 ICH E2B/M2)
Parent Route of administration	(B.4.k.9 ICH E2B/M2)

will be submitted according to the codes specified by ICH M2 for the values specified by ICH E2B.

- **Pharmaceutical form (Dosage form)**

The data item:

Pharmaceutical form (Dosage form)	(B.4.k.7 ICH E2B/M2)
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will be submitted according the terminology as defined in the 'Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers' as published by the Council of Europe.

- **Dose units**

The data item:

Dose unit	(B.4.k.5.2 ICH E2B/M2)
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will be submitted according to the codes specified by ICH M2 for the values specified by ICH E2B.

- **Country codes**

The data items:

Identification of the country of the primary source	(A.1.1 ICH E2B/M2)
Identification of the country where the reaction / event occurred	(A.1.2 ICH E2B/M2)
Reporter's country	(A.2.1.3 ICH E2B/M2)
Sender's country code	(A.3.1.4e ICH E2B/M2)
Receiver's country code	(A.3.2.3e ICH E2B/M2)
Country of authorisation / application	(B.4.k.4.2 ICH E2B/M2)

will be submitted according to the codes specified by ICH M2 for the values specified by ICH E2B.

- **Other codes**

Other data elements will be sent with controlled codes as reflected in the ICH M2 Specification of the Message for the Electronic Transmission of Individual Case Safety Reports.

5.2 **Veterinary Medicinal Products Veterinary Medicinal Product terms**

The data items:

Veterinary Medicinal Product Name	
Active Substance(s)	
ATCvet Code	

in the Safety Report message will be provided for centrally authorised veterinary medicinal products in compliance with the Community Register of Veterinary Medicinal Products published in accordance with Article 34 of Council Regulation (EEC) N°2309/93; active substance(s) and ATCvet Codes which are not included in the Community Register will be submitted in compliance with the ATCvet classification as provided by the Nordic Council of Europe.

- **Human Adverse Reaction terms**

The data items:

Reaction term	
Reason for treatment	
Previous adverse reaction term	

will be provided in compliance with an agreed terminology (if appropriate, LLT numeric code or English term of the MedDRA medical dictionary)

- **Veterinary Adverse Reaction terms**

The data items:

Reaction term	
Reason for treatment	
Previous reaction term	

will be provided in compliance with the LLT numeric code or English term of the VEDDRA Reaction List.

- **Animal Species**

The data item:

Species	
Authorised Target Animal Species	

will be provided in compliance with the VEDDRA Species List as adopted by the Veterinary Pharmacovigilance Working Party (PhVWP) on behalf of the CVMP.

- **Routes of administration**

The data item:

Route of administration	
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will be provided in compliance with the definitions of the ‘Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers’ as published by the Council of Europe.

- **Pharmaceutical form (Dosage form)**

The data item:

Pharmaceutical form	
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will be provided in compliance with the definitions of the ‘Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers’ as published by the Council of Europe.

- **Dose units**

The data item:

Dose unit of treatment given	
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will be submitted according to the codes specified by ICH M2 for the values specified by ICH E2B.

- **Country codes**

The data items:

Reporting Country	
Purchase Country	
Reporter Country	
Sender Country	
Receiver Country	

will be submitted according to the codes specified by ICH M2 for the values specified by ICH E2B.

- **Other codes**

Other data elements should be sent with controlled codes as reflected in the ‘Data Elements for the Electronic Transmission of Veterinary Individual Case Safety Reports’ based on Part II, Chapter 1 *Pharmacovigilance for Veterinary Medicinal Products*

6. Acknowledgement of Safety Reports

The receiver of Safety Messages will acknowledge the electronic receipt of Safety Reports by means of the Acknowledgement message according to the ICH M2 specification ‘Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR Version 2.0 or future releases)’ and the Veterinary Guidelines.

The objective of an acknowledgement is to verify the usability and compliance of the transmitted data as per ICH recommendations or Veterinary Guidelines. It also permits the sender to track and correct errors, if any, prior to the re-transmission.

7. Registration Process for the Electronic Transmission of Individual Case Safety Reports (ICSRs)

Expedited Safety Reports and Periodic Safety Updates will be sent electronically through electronic data interchange (EDI) e.g. E-mail or by CD-ROM/Floppy disk.

Postal delivery services will be used for submissions using physical media. The postal or special delivery receipt will constitute proof of receipt.

Messages transmitted via EDI will be replied to the sender organisation by an acknowledgement with feedback on the data receipt.

The following steps will be followed in order to register and obtain certification to transmit information to the Agency and/or National competent authorities previous to the electronic submission of Safety Reports:

1. Contact the Electronic Safety Reporting co-ordinator

Contact the Electronic Safety Reporting co-ordinator at the Agency and/or the national competent authorities. Information about the responsible contact person(s) will be published on the Agency/EudraNet homepage.

2. Send Letter of Intent

Send a Letter of Intent for the Electronic Submission of Safety Reports to the Agency and/or National competent authorities. A template will be available on the Agency/EudraNet homepage.

3. Submit Implementation Plan

Submit an implementation plan indicating the approach to the generation and transmission of Electronic Safety Messages in accordance with the ICH guidelines and the requirements as defined in this chapter.

4. Review of the Implementation Plan

Review the project plan with the Electronic Safety Reporting co-ordinator at the Agency and/or National competent authorities. If necessary a meeting can be arranged to outline the specific requirements and to clarify open questions.

5. Obtain certification (for Internet communication)

6. Adopt and sign the Interchange Agreement

Agree and sign the Interchange Agreement specifying criteria for message identification, sender identification, receiver identification, acknowledgement of reports, minimum information to be submitted in one report.

Agree on methods and tools to guarantee secure transmission and processing of information.

A form will be available on the Agency/EudraNet homepage.

7. Test phase

Prepare Safety Message files in accordance with the ICH M2 recommendations and ICH E2B guidelines/Veterinary guidelines as well as the definitions and specifications set out in this document.

Test the correctness of the SGML files before transmission to ensure compliance with ICH ICSR M2/Veterinary specifications: syntax, field lengths, minimum information, data dictionaries compliance.

8. *Operational phase*

Start operational transmission of Safety Reports upon successful completion of the test phase.

8. Electronic Submission of Periodic Safety Update Reports (PSURs)

Periodic Safety Update Reports will be submitted electronically when the corresponding specification has been adopted by the ICH secretariat and the CPMP and CVMP.

However, until such a time, a full or partial electronic submission of PSURs, which have to follow the specifications of ICH E2C, may be discussed with the competent authorities in Member States and/or the Agency. Format and method of the electronic submission need to be agreed between the MAH and the national competent authority and/or the Agency.

Complete case reports of the line listing of spontaneously reported listed reactions that have been collected will be submitted electronically according to the ICH E2B/M2 ICSR Specifications and Veterinary Guidelines upon request by a competent authority.

For the registration process related to the electronic transmission of PSURs please refer to Section 7 of this Chapter.

ANNEX I - VEDDRA list of Clinical Terms (EMEA/CVMP/413 /99-Final)

Number	SOC	HLT	PT	LLT
1	Application site disorders	Application site reactions	Application site abscess	Application site abscess
2	Application site disorders	Application site reactions	Application site alopecia	Application site alopecia
3	Application site disorders	Application site reactions	Application site alopecia	Application site hair loss
4	Application site disorders	Application site reactions	Application site blister	Application site blister
5	Application site disorders	Application site reactions	Application site erythema	Application site erythema
6	Application site disorders	Application site reactions	Application site erythema	Application site rubra
7	Application site disorders	Application site reactions	Application site granuloma	Application site granuloma
8	Application site disorders	Application site reactions	Application site haematoma	Application site bruising
9	Application site disorders	Application site reactions	Application site haematoma	Application site petechiae
10	Application site disorders	Application site reactions	Application site haematoma	Application site haematoma
11	Application site disorders	Application site reactions	Application site haemorrhage	Application site haemorrhage
12	Application site disorders	Application site reactions	Application site haemorrhage	Application site bleeding
13	Application site disorders	Application site reactions	Application site inflammation	Application site inflammation
14	Application site disorders	Application site reactions	Application site lesion	Application site lesion
15	Application site disorders	Application site reactions	Application site lesion	Application site scab
16	Application site disorders	Application site reactions	Application site lesion	Application site crust
17	Application site disorders	Application site reactions	Application site mucopurulent	Application site mucopurulent

		discharge	discharge
18 Application site disorders	Application site reactions	Application site necrosis	Application site necrosis
19 Application site disorders	Application site reactions	Application site oedema	Application site oedema
20 Application site disorders	Application site reactions	Application site oedema	Application site swelling
21 Application site disorders	Application site reactions	Application site oedema	Application site lump
22 Application site disorders	Application site reactions	Application site pain	Application site pain
23 Application site disorders	Application site reactions	Application site pruritus	Application site itching
24 Application site disorders	Application site reactions	Application site pruritus	Application site irritation
25 Application site disorders	Application site reactions	Application site pruritus	Application site pruritus
26 Application site disorders	Application site reactions	Application site pruritus	Application site scratching
27 Application site disorders	Application site reactions	Application site pyoderma	Application site pustules
28 Application site disorders	Application site reactions	Application site pyoderma	Application site pyoderma
29 Application site disorders	Application site reactions	Application site reaction NOS	Application site reaction NOS
30 Application site disorders	Application site reactions	Application site sarcoma	Application site sarcoma
31 Application site disorders	Application site reactions	Application site self trauma	Application site self trauma
32 Application site disorders	Application site reactions	Application site serosanguinous discharge	Application site weeping (see also 'skin')
33 Application site disorders	Application site reactions	Application site serosanguinous discharge	Application site serosanguinous discharge
34 Application site disorders	Application site reactions	Application site serous discharge	Application site serous discharge

35 Application site disorders	Application site reactions	Application site ulcer	Application site ulcer
36 Application site disorders	Implant site reactions	Implant site abscess	Implant site abscess
37 Application site disorders	Implant site reactions	Implant site alopecia	Implant site alopecia
38 Application site disorders	Implant site reactions	Implant site alopecia	Implant site hair loss
39 Application site disorders	Implant site reactions	Implant site blister	Implant site blister
40 Application site disorders	Implant site reactions	Implant site erythema	Implant site rubra
41 Application site disorders	Implant site reactions	Implant site erythema	Implant site erythema
42 Application site disorders	Implant site reactions	Implant site granuloma	Implant site granuloma
43 Application site disorders	Implant site reactions	Implant site haematoma	Implant site bruising
44 Application site disorders	Implant site reactions	Implant site haematoma	Implant site haematoma
45 Application site disorders	Implant site reactions	Implant site haematoma	Implant site petechiae
46 Application site disorders	Implant site reactions	Implant site haemorrhage	Implant site haemorrhage
47 Application site disorders	Implant site reactions	Implant site haemorrhage	Implant site bleeding
48 Application site disorders	Implant site reactions	Implant site inflammation	Implant site inflammation
49 Application site disorders	Implant site reactions	Implant site lesion	Implant site scab
50 Application site disorders	Implant site reactions	Implant site lesion	Implant site lesion
51 Application site disorders	Implant site reactions	Implant site lesion	Implant site crust
52 Application site disorders	Implant site reactions	Implant site mucopurulent discharge	Implant site mucopurulent discharge
53 Application site disorders	Implant site reactions	Implant site necrosis	Implant site necrosis

54 Application site disorders	Implant site reactions	Implant site oedema	Implant site lump
55 Application site disorders	Implant site reactions	Implant site oedema	Implant site oedema
56 Application site disorders	Implant site reactions	Implant site oedema	Implant site swelling
57 Application site disorders	Implant site reactions	Implant site pain	Implant site pain
58 Application site disorders	Implant site reactions	Implant site pruritus	Implant site irritation
59 Application site disorders	Implant site reactions	Implant site pruritus	Implant site itching
60 Application site disorders	Implant site reactions	Implant site pruritus	Implant site scratching
61 Application site disorders	Implant site reactions	Implant site pruritus	Implant site pruritus
62 Application site disorders	Implant site reactions	Implant site pyoderma	Implant site pustules
63 Application site disorders	Implant site reactions	Implant site pyoderma	Implant site pyoderma
64 Application site disorders	Implant site reactions	Implant site reaction NOS	Implant site reaction NOS
65 Application site disorders	Implant site reactions	Implant site sarcoma	Implant site sarcoma
66 Application site disorders	Implant site reactions	Implant site self trauma	Implant site self trauma
67 Application site disorders	Implant site reactions	Implant site serosanguinous discharge	Implant site weeping (see also 'skin')
68 Application site disorders	Implant site reactions	Implant site serosanguinous discharge	Implant site serosanguinous discharge
69 Application site disorders	Implant site reactions	Implant site serous discharge	Implant site serous discharge
70 Application site disorders	Implant site reactions	Implant site ulcer	Implant site ulcer
71 Application site disorders	Implant site reactions	Movement of implant	Movement of implant

72 Application site disorders	Injection site reactions	Injection site abscess	Injection site abscess
73 Application site disorders	Injection site reactions	Injection site alopecia	Injection site alopecia
74 Application site disorders	Injection site reactions	Injection site alopecia	Injection site hair loss
75 Application site disorders	Injection site reactions	Injection site blister	Injection site blister
76 Application site disorders	Injection site reactions	Injection site erythema	Injection site rubra
77 Application site disorders	Injection site reactions	Injection site erythema	Injection site erythema
78 Application site disorders	Injection site reactions	Injection site granuloma	Injection site granuloma
79 Application site disorders	Injection site reactions	Injection site haematoma	Injection site bruising
80 Application site disorders	Injection site reactions	Injection site haematoma	Injection site haematoma
81 Application site disorders	Injection site reactions	Injection site haematoma	Injection site petechiae
82 Application site disorders	Injection site reactions	Injection site haemorrhage	Injection site haemorrhage
83 Application site disorders	Injection site reactions	Injection site haemorrhage	Injection site bleeding
84 Application site disorders	Injection site reactions	Injection site inflammation	Injection site inflammation
85 Application site disorders	Injection site reactions	Injection site lesion	Injection site scab
86 Application site disorders	Injection site reactions	Injection site lesion	Injection site lesion
87 Application site disorders	Injection site reactions	Injection site lesion	Injection site crust
88 Application site disorders	Injection site reactions	Injection site mucopurulent discharge	Injection site mucopurulent discharge
89 Application site disorders	Injection site reactions	Injection site necrosis	Injection site necrosis
90 Application site disorders	Injection site reactions	Injection site oedema	Injection site oedema

91 Application site disorders	Injection site reactions	Injection site oedema	Injection site swelling
92 Application site disorders	Injection site reactions	Injection site oedema	Injection site lump
93 Application site disorders	Injection site reactions	Injection site pain	Injection site pain
94 Application site disorders	Injection site reactions	Injection site pruritus	Injection site irritation
95 Application site disorders	Injection site reactions	Injection site pruritus	Injection site itching
96 Application site disorders	Injection site reactions	Injection site pruritus	Injection site scratching
97 Application site disorders	Injection site reactions	Injection site pruritus	Injection site pruritus
98 Application site disorders	Injection site reactions	Injection site pyoderma	Injection site pustules
99 Application site disorders	Injection site reactions	Injection site pyoderma	Injection site pyoderma
100 Application site disorders	Injection site reactions	Injection site reaction NOS	Injection site reaction NOS
101 Application site disorders	Injection site reactions	Injection site sarcoma	Injection site sarcoma
102 Application site disorders	Injection site reactions	Injection site self trauma	Injection site self trauma
103 Application site disorders	Injection site reactions	Injection site serosanguinous discharge	Injection site weeping (see also 'skin')
104 Application site disorders	Injection site reactions	Injection site serosanguinous discharge	Injection site serosanguinous discharge
105 Application site disorders	Injection site reactions	Injection site serous discharge	Injection site serous discharge
106 Application site disorders	Injection site reactions	Injection site ulcer	Injection site ulcer
107 Behavioural disorders	Fish behavioural disorders	Abnormal swimming in fish	Abnormal swimming in fish
108 Behavioural disorders	Fish behavioural disorders	Leaping behaviour in fish	Leaping behaviour in fish

109	Behavioural disorders	Miscellaneous eating disorders NOS	Miscellaneous eating disorder NOS	Miscellaneous eating disorder NOS
110	Behavioural disorders	Other behavioural disorders	Somnolence	Sedated
111	Behavioural disorders	Other behavioural disorders	Aggression	Biting
112	Behavioural disorders	Other behavioural disorders	Aggression	Aggression
113	Behavioural disorders	Other behavioural disorders	Anxiety	Distress
114	Behavioural disorders	Other behavioural disorders	Anxiety	Anxiety
115	Behavioural disorders	Other behavioural disorders	Behavioural disorder NOS	Behavioural disorder NOS
116	Behavioural disorders	Other behavioural disorders	Hallucination	Hallucination
117	Behavioural disorders	Other behavioural disorders	Hyperactivity	Hyperactivity
118	Behavioural disorders	Other behavioural disorders	Hyperactivity	Restlessness
119	Behavioural disorders	Other behavioural disorders	Hyperactivity	Excitation
120	Behavioural disorders	Other behavioural disorders	Hyperactivity	Agitation
121	Behavioural disorders	Other behavioural disorders	Hyperactivity	Hyperexcitation
122	Behavioural disorders	Other behavioural disorders	Inappropriate defaecation	Inappropriate defaecation
123	Behavioural disorders	Other behavioural disorders	Inappropriate urination	Inappropriate urination
124	Behavioural disorders	Other behavioural disorders	Self trauma	Self trauma
125	Behavioural disorders	Other behavioural disorders	Somnolence	Somnolence
126	Behavioural disorders	Other behavioural disorders	Somnolence	Dullness

127 Behavioural disorders	Other behavioural disorders	Somnolence	Sleepy
128 Behavioural disorders	Other behavioural disorders	Teeth grinding	Teeth grinding
129 Behavioural disorders	Other behavioural disorders	Vocalisation	Vocalisation
130 Behavioural disorders	Other behavioural disorders	Vocalisation	Crying
131 Behavioural disorders	Other behavioural disorders	Vocalisation	Mewing
132 Behavioural disorders	Other behavioural disorders	Vocalisation	Barking
133 Behavioural disorders	Pica	Coprophagia	Coprophagia
134 Behavioural disorders	Pica	Pica NOS	Pica NOS
135 Behavioural disorders	Pica	Pica NOS	Licking
136 Behavioural disorders	Pica	Polyphagia	Excessive appetite (see 'Systemic' for loss of appetite)
137 Behavioural disorders	Pica	Polyphagia	Polyphagia
138 Behavioural disorders	Sexual disorders NOS	Sexual disorder NOS	Sexual disorder NOS (see 'Reproductive' for named sexual disorders)
139 Behavioural disorders	Sleep disorders	Insomnia	Insomnia
140 Behavioural disorders	Sleep disorders	Insomnia	Not sleeping
141 Behavioural disorders	Sleep disorders	Sleep disorder NOS	Sleep disorder NOS
142 Blood and lymphatic system disorders	Anaemia	Anaemia NOS	Anaemia NOS
143 Blood and lymphatic system	Anaemia	Anaemia NOS	Drug-induced anaemia

	disorders			
144	Blood and lymphatic system disorders	Anaemia	Anaemia NOS	Iron deficiency anaemia eg in piglets
145	Blood and lymphatic system disorders	Anaemia	Aplastic anaemia	Non-regenerative anaemia
146	Blood and lymphatic system disorders	Anaemia	Aplastic anaemia	Aplastic anaemia
147	Blood and lymphatic system disorders	Anaemia	Haemolytic anaemia	Haemolytic anaemia
148	Blood and lymphatic system disorders	Blood and lymphatic system disorders NOS	Blood and lymphatic system disorder NOS	Blood and lymphatic system disorder NOS
149	Blood and lymphatic system disorders	Bone marrow aplasia	Bone marrow aplasia	Bone marrow aplasia
150	Blood and lymphatic system disorders	Bone marrow aplasia	Bone marrow aplasia	Bone marrow suppression
151	Blood and lymphatic system disorders	Coagulation abnormalities	Other coagulation abnormalities	Prolonged bleeding
152	Blood and lymphatic system disorders	Coagulation abnormalities	Other coagulation abnormalities	Other coagulation abnormality NOS
153	Blood and lymphatic system disorders	Coagulation abnormalities	Thrombosis	Blood clots
154	Blood and lymphatic system disorders	Coagulation abnormalities	Thrombosis	Disseminated intravascular coagulation
155	Blood and lymphatic system disorders	Coagulation abnormalities	Thrombosis	Thromboemboli

156 Blood and lymphatic system disorders	Coagulation abnormalities	Thrombosis	Thrombosis
157 Blood and lymphatic system disorders	Congenital haematological disorders	Congenital coagulopathy NOS	Congenital coagulopathy NOS
158 Blood and lymphatic system disorders	Congenital haematological disorders	Congenital haematological disorder NOS	Congenital haematological disorder NOS
159 Blood and lymphatic system disorders	Congenital haematological disorders	Haemophilia	Haemophilia
160 Blood and lymphatic system disorders	Disorders of platelets and coagulopathies	Thrombocytopenia	Thrombocytopenia
161 Blood and lymphatic system disorders	Disorders of platelets and coagulopathies	Thrombocytopenia	Low platelet count
162 Blood and lymphatic system disorders	Disorders of white blood cells	Eosinophilia	Eosinophilia
163 Blood and lymphatic system disorders	Disorders of white blood cells	Leucocytosis	Leucocytosis
164 Blood and lymphatic system disorders	Disorders of white blood cells	Leucopenia	Leucopenia
165 Blood and lymphatic system disorders	Disorders of white blood cells	Lymphocytosis	Lymphocytosis
166 Blood and lymphatic system disorders	Disorders of white blood cells	Lymphopenia	Lymphopenia
167 Blood and lymphatic system disorders	Disorders of white blood cells	Neutropenia	Neutropenia
168 Blood and lymphatic system	Disorders of white blood cells	Neutrophilia	Neutrophilia

disorders

169 Blood and lymphatic system disorders	Disorders of white blood cells	Panleucopenia	Panleucopenia
170 Blood and lymphatic system disorders	Haemopoietic neoplasms	Haemopoietic neoplasm NOS	Haemopoietic neoplasm NOS
171 Blood and lymphatic system disorders	Haemopoietic neoplasms	Leukaemia	Leukaemia
172 Blood and lymphatic system disorders	Haemopoietic neoplasms	Lymphosarcoma	Lymphosarcoma
173 Blood and lymphatic system disorders	Lymph node disorders	Lymphadenitis	Lymphadenitis
174 Blood and lymphatic system disorders	Lymph node disorders	Lymphadenopathy	Lymphadenopathy
175 Blood and lymphatic system disorders	Lymph node disorders	Lymphangitis	Lymphangitis
176 Blood and lymphatic system disorders	Lymph node disorders	Lymphoma	Lymphoma
177 Blood and lymphatic system disorders	Other blood disorders	Haemorrhage NOS	Haemorrhage NOS
178 Blood and lymphatic system disorders	Other blood disorders	Haemorrhage NOS	Profuse bleeding
179 Blood and lymphatic system disorders	Other blood disorders	Haemostasis	Haemostasis
180 Blood and lymphatic system disorders	Other blood disorders	Hypoalbuminaemia	Hypoalbuminaemia

181	Blood and lymphatic system disorders	Other blood disorders	Red blood cell disorder NOS	Red blood cell disorder NOS
182	Blood and lymphatic system disorders	Spleen and reticulo-endothelial system disorders	Spleen and reticulo-endothelial system disorder NOS	Spleen and reticulo-endothelial system disorder NOS
183	Blood and lymphatic system disorders	Spleen and reticulo-endothelial system disorders	Spleen rupture	Spleen rupture
184	Blood and lymphatic system disorders	Spleen and reticulo-endothelial system disorders	Splenitis	Splenitis
185	Blood and lymphatic system disorders	Spleen and reticulo-endothelial system disorders	Splenomegaly	Splenomegaly
186	Cardio-vascular system disorders	Cardiac rhythm disorders	Arrhythmia	Arrhythmia
187	Cardio-vascular system disorders	Cardiac rhythm disorders	Arrhythmia	Atrial fibrillation
188	Cardio-vascular system disorders	Cardiac rhythm disorders	Bradycardia	Bradycardia
189	Cardio-vascular system disorders	Cardiac rhythm disorders	Bradycardia	Decreased heart rate
190	Cardio-vascular system disorders	Cardiac rhythm disorders	Bradycardia	Slow heart rate
191	Cardio-vascular system disorders	Cardiac rhythm disorders	Heart block	Heart block
192	Cardio-vascular system disorders	Cardiac rhythm disorders	Tachycardia	Tachycardia
193	Cardio-vascular system disorders	Cardiac rhythm disorders	Tachycardia	Increased heart rate
194	Cardio-vascular system disorders	Cardiac rhythm disorders	Tachycardia	Elevated heart rate
195	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Cardiac arrest	Cardiac arrest

196	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Cardiac arrest	Cardiac failure
197	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Cardiac arrest	Heart failure
198	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Cardiac arrest	Heart stop
199	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Heart disease aggravated	Heart disease aggravated
200	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Heart disease aggravated	Heart insufficiency
201	Cardio-vascular system disorders	Cardiac/heart disease aggravated	Heart disease aggravated	Heart valve opening
202	Cardio-vascular system disorders	Cardiac/heart disease signs	Cardiac disease signs NOS	Cardiac disease signs NOS
203	Cardio-vascular system disorders	Cardiac/heart disease signs	Cardiac enlargement	Right ventricular dilatation
204	Cardio-vascular system disorders	Cardiac/heart disease signs	Cardiac enlargement	Cardiac enlargement
205	Cardio-vascular system disorders	Cardiac/heart disease signs	Cardiomyopathy	Cardiomyopathy
206	Cardio-vascular system disorders	Cardiac/heart disease signs	Carditis	Carditis
207	Cardio-vascular system disorders	Cardiac/heart disease signs	Carditis	Heart inflammation
208	Cardio-vascular system disorders	Cardiac/heart disease signs	Embolism	Embolism
209	Cardio-vascular system disorders	Cardiac/heart disease signs	Endocardial fibroelastosis	Endocardial fibroelastosis
210	Cardio-vascular system disorders	Cardiac/heart disease signs	Endocarditis	Endocarditis
211	Cardio-vascular system disorders	Cardiac/heart disease signs	Infarction	Infarction

212	Cardio-vascular system disorders	Cardiac/heart disease signs	Murmur	Cardiac murmur
213	Cardio-vascular system disorders	Cardiac/heart disease signs	Murmur	Heart murmur
214	Cardio-vascular system disorders	Cardiac/heart disease signs	Murmur	Murmur
215	Cardio-vascular system disorders	Cardiac/heart disease signs	Myocarditis	Myocarditis
216	Cardio-vascular system disorders	Cardiac/heart disease signs	Pericarditis	Pericarditis
217	Cardio-vascular system disorders	Cardiac/heart disease signs	Valvular disorders	Valvular insufficiency
218	Cardio-vascular system disorders	Circulatory disorders	Circulatory shock	Cardiopulmonary stop
219	Cardio-vascular system disorders	Circulatory disorders	Circulatory shock	Shock
220	Cardio-vascular system disorders	Circulatory disorders	Circulatory shock	Circulatory shock
221	Cardio-vascular system disorders	Circulatory disorders	Circulatory shock	Pale mucous membranes
222	Cardio-vascular system disorders	Circulatory disorders	Circulatory shock	Circulatory collapse
223	Cardio-vascular system disorders	Circulatory disorders	Hypertension	Hypertension
224	Cardio-vascular system disorders	Circulatory disorders	Hypertension	High blood pressure
225	Cardio-vascular system disorders	Circulatory disorders	Hypotension	Syncope
226	Cardio-vascular system disorders	Circulatory disorders	Hypotension	Fainting
227	Cardio-vascular system disorders	Circulatory disorders	Hypotension	Hypotension
228	Cardio-vascular system disorders	Circulatory disorders	Hypotension	Low blood pressure
229	Cardio-vascular system disorders	Circulatory disorders	Ischaemia	Ischaemia
230	Cardio-vascular system disorders	Congenital cardiovascular	Aortic stenosis	Aortic stenosis

	disorders			
231	Cardio-vascular system disorders	Congenital cardiovascular disorders	Congenital cardiovascular disorder NOS	Congenital cardiovascular disorder NOS
232	Cardio-vascular system disorders	Congenital cardiovascular disorders	Ductus botalli persistence	Ductus botalli persistence
233	Cardio-vascular system disorders	Congenital cardiovascular disorders	Pulmonary stenosis	Pulmonary stenosis
234	Cardio-vascular system disorders	Congenital cardiovascular disorders	Ventricular septal defects	Ventricular septal defects
235	Cardio-vascular system disorders	Pericardial disease	Cardiac tamponade	Cardiac tamponade
236	Cardio-vascular system disorders	Pericardial disease	Pericardial effusion	Pericardial effusion
237	Cardio-vascular system disorders	Pericardial disease	Pericardial haemorrhage	Pericardial haemorrhage
238	Cardio-vascular system disorders	Pericardial disease	Pericarditis	Pericarditis
239	Cardio-vascular system disorders	Vascular disease signs	Aortic degeneration	Aortic degeneration
240	Cardio-vascular system disorders	Vascular disease signs	Arteritis	Arteritis
241	Cardio-vascular system disorders	Vascular disease signs	Phlebitis	Phlebitis
242	Cardio-vascular system disorders	Vascular disease signs	Vascular dilation and rupture	Aneurism
243	Cardio-vascular system disorders	Vascular disease signs	Vascular dilation and rupture	Aortic rupture
244	Cardio-vascular system disorders	Vascular disease signs	Vascular dilation and rupture	Vascular rupture
245	Cardio-vascular system disorders	Vascular disease signs	Vascular disease sign NOS	Vascular disease sign NOS (see also endocarditis)

246	Cardio-vascular system disorders	Vascular disease signs	Vasculitis	Vasculitis
247	Cardio-vascular system disorders	Vascular disease signs	Vasculitis	Perivascular necrosis
248	Cardio-vascular system disorders	Vascular disease signs	Vasculitis	Vascular spasm
249	Cardio-vascular system disorders	Vascular disease signs	Vasculitis	Vascular inflammation
250	Digestive tract disorders	Abdominal cavity disorders	Abdominal cavity disorder NOS	Abdominal cavity disorder NOS
251	Digestive tract disorders	Abdominal cavity disorders	Abdominal cavity hernia	Abdominal cavity hernia
252	Digestive tract disorders	Abdominal cavity disorders	Peritonitis	Peritonitis
253	Digestive tract disorders	Abdominal cavity disorders	Peritonitis	Omentum inflammation
254	Digestive tract disorders	Anal and rectal disorders	Perineal fistula	Perineal fistula
255	Digestive tract disorders	Anal and rectal disorders	Rectal prolapse	Anal prolapse
256	Digestive tract disorders	Anal and rectal disorders	Rectal prolapse	Rectal prolapse
257	Digestive tract disorders	Digestive tract congenital disorders	Atresia ani	Absence of anus
258	Digestive tract disorders	Digestive tract congenital disorders	Atresia ani	Atresia ani
259	Digestive tract disorders	Digestive tract congenital disorders	Digestive tract congenital disorder NOS	Digestive tract congenital disorder NOS
260	Digestive tract disorders	Fish digestive tract disorders	Swim bladder disorder	Swim bladder disorder
261	Digestive tract disorders	Large intestine disorders	Abdominal pain	Abdominal cramps
262	Digestive tract disorders	Large intestine disorders	Abdominal pain	Abdominal pain

263 Digestive tract disorders	Large intestine disorders	Abdominal pain	Colic
264 Digestive tract disorders	Large intestine disorders	Colitis	Colitis
265 Digestive tract disorders	Large intestine disorders	Constipation	Faecal impaction
266 Digestive tract disorders	Large intestine disorders	Constipation	Constipation
267 Digestive tract disorders	Large intestine disorders	Diverticular disorders	Diverticular disorders
268 Digestive tract disorders	Large intestine disorders	Flatulence	Flatulence
269 Digestive tract disorders	Large intestine disorders	Involuntary defecation	Involuntary defecation
270 Digestive tract disorders	Large intestine disorders	Rectal haemorrhage	Rectal haemorrhage
271 Digestive tract disorders	Large intestine disorders	Rectal haemorrhage	Rectal bleeding
272 Digestive tract disorders	Large intestine disorders	Tenesmus	Tenesmus
273 Digestive tract disorders	Oesophageal and pharyngeal disorders	Megaoesophagus	Megaoesophagus
274 Digestive tract disorders	Oesophageal and pharyngeal disorders	Oesophageal paralysis	Oesophageal paralysis
275 Digestive tract disorders	Oesophageal and pharyngeal disorders	Oesophagitis	Oesophagitis
276 Digestive tract disorders	Oesophageal and pharyngeal disorders	Oesophagus obstruction	Oesophagus obstruction
277 Digestive tract disorders	Oesophageal and pharyngeal disorders	Oesophagus perforation	Oesophagus perforation
278 Digestive tract disorders	Oesophageal and pharyngeal disorders	Pharyngeal disorders	Pharyngitis

279 Digestive tract disorders	Oesophageal and pharyngeal disorders	Pharyngeal disorders	Pharyngeal ulceration
280 Digestive tract disorders	Oral cavity disorders	Dental discolouration	Discoloured teeth
281 Digestive tract disorders	Oral cavity disorders	Dental discolouration	Dental discolouration
282 Digestive tract disorders	Oral cavity disorders	Dysphagia	Impaired swallowing
283 Digestive tract disorders	Oral cavity disorders	Dysphagia	Dysphagia
284 Digestive tract disorders	Oral cavity disorders	Gingivitis	Gingivitis
285 Digestive tract disorders	Oral cavity disorders	Gingivitis	Pyorrhoea
286 Digestive tract disorders	Oral cavity disorders	Glossitis	Tongue inflammation
287 Digestive tract disorders	Oral cavity disorders	Glossitis	Glossitis
288 Digestive tract disorders	Oral cavity disorders	Glossitis	Tongue ulceration
289 Digestive tract disorders	Oral cavity disorders	Halitosis	Halitosis
290 Digestive tract disorders	Oral cavity disorders	Hypersalivation	Drooling
291 Digestive tract disorders	Oral cavity disorders	Hypersalivation	Hypersalivation
292 Digestive tract disorders	Oral cavity disorders	Hyposalivation	Oral dryness
293 Digestive tract disorders	Oral cavity disorders	Hyposalivation	Dry mouth
294 Digestive tract disorders	Oral cavity disorders	Oral haemorrhage	Oral haemorrhage
295 Digestive tract disorders	Oral cavity disorders	Oral haemorrhage	Oral bleeding
296 Digestive tract disorders	Oral cavity disorders	Stomatitis	Buccal ulceration

297 Digestive tract disorders	Oral cavity disorders	Stomatitis	Buccal irritation
298 Digestive tract disorders	Oral cavity disorders	Stomatitis	Stomatitis
299 Digestive tract disorders	Oral cavity disorders	Stomatitis	Oral ulceration
300 Digestive tract disorders	Other digestive tract disorders	Diarrhoea	Diarrhoea
301 Digestive tract disorders	Other digestive tract disorders	Diarrhoea	Scours
302 Digestive tract disorders	Other digestive tract disorders	Diarrhoea	Loose stools
303 Digestive tract disorders	Other digestive tract disorders	Digestive tract disorder NOS	Digestive tract disorder NOS
304 Digestive tract disorders	Other digestive tract disorders	Digestive tract haemorrhage NOS	Digestive tract haemorrhage NOS
305 Digestive tract disorders	Other digestive tract disorders	Digestive tract neoplasm NOS	Digestive tract neoplasm NOS
306 Digestive tract disorders	Other digestive tract disorders	Digestive tract stasis	Digestive tract stasis
307 Digestive tract disorders	Other digestive tract disorders	Digestive tract stasis	Ruminal stasis
308 Digestive tract disorders	Other digestive tract disorders	Digestive tract stenosis and obstruction NOS	Digestive tract stenosis and obstruction NOS
309 Digestive tract disorders	Other digestive tract disorders	Digestive tract tympany	Digestive tract tympany
310 Digestive tract disorders	Other digestive tract	Distension of abdomen	Distension of abdomen

	disorders		
311 Digestive tract disorders	Other digestive tract disorders	Gastroenteritis	Gastroenteritis
312 Digestive tract disorders	Other digestive tract disorders	Haemorrhagic diarrhoea	Haemorrhagic diarrhoea
313 Digestive tract disorders	Other digestive tract disorders	Haemorrhagic diarrhoea	Bloody diarrhoea
314 Digestive tract disorders	Other digestive tract disorders	Haemorrhagic gastroenteritis	Haemorrhagic gastroenteritis
315 Digestive tract disorders	Other digestive tract disorders	Melaena	Melaena
316 Digestive tract disorders	Other digestive tract disorders	Melaena	Tarry or black stool (see also diarrhoea)
317 Digestive tract disorders	Ruminant stomach disorders	Abomasitis	Abomasitis
318 Digestive tract disorders	Ruminant stomach disorders	Bloat	Bloat
319 Digestive tract disorders	Ruminant stomach disorders	Reticulitis	Reticulitis
320 Digestive tract disorders	Ruminant stomach disorders	Rumenitis	Rumenitis
321 Digestive tract disorders	Ruminant stomach disorders	Ruminant stomach disorders	Displaced abomasum
322 Digestive tract disorders	Small intestine disorders	Digestive tract malabsorption disorder NOS	Digestive tract malabsorption disorder NOS
323 Digestive tract disorders	Small intestine disorders	Duodenitis	Duodenitis
324 Digestive tract disorders	Small intestine disorders	Enteritis	Intestinal congestion

325 Digestive tract disorders	Small intestine disorders	Enteritis	Enteritis
326 Digestive tract disorders	Small intestine disorders	Ileitis	Ileitis
327 Digestive tract disorders	Small intestine disorders	Intussusception	Intussusception
328 Digestive tract disorders	Small intestine disorders	Pancreas exocrine disorder	Exocrine pancreatitis
329 Digestive tract disorders	Small intestine disorders	Pancreas exocrine disorder NOS	Pancreas exocrine disorder NOS
330 Digestive tract disorders	Small intestine disorders	Paralytic ileus	Paralytic ileus
331 Digestive tract disorders	Stomach disorders	Emesis	Vomiting
332 Digestive tract disorders	Stomach disorders	Emesis	Emesis
333 Digestive tract disorders	Stomach disorders	Eructation	Eructation
334 Digestive tract disorders	Stomach disorders	Eructation	Belching
335 Digestive tract disorders	Stomach disorders	Gastric torsion	Gastric torsion
336 Digestive tract disorders	Stomach disorders	Gastric torsion	Gastric volvulus
337 Digestive tract disorders	Stomach disorders	Gastric ulceration	Gastric ulceration
338 Digestive tract disorders	Stomach disorders	Gastritis	Gastritis
339 Digestive tract disorders	Stomach disorders	Haematemesis	Haematemesis
340 Digestive tract disorders	Stomach disorders	Haematemesis	Blood in vomit
341 Digestive tract disorders	Stomach disorders	Retching	Gagging
342 Digestive tract disorders	Stomach disorders	Retching	Retching
343 Ear and labyrinth disorders	Congenital ear disorders	Congenital ear disorder NOS	Congenital ear disorder NOS

344 Ear and labyrinth disorders	Ear disorders NOS	Ear pain	Ear pain
345 Ear and labyrinth disorders	Ear disorders NOS	Otorrhoea	Otorrhoea
346 Ear and labyrinth disorders	Ear disorders NOS	Otorrhoea	Ear discharge
347 Ear and labyrinth disorders	External ear disorders	Aural haematoma	Aural haematoma
348 Ear and labyrinth disorders	External ear disorders	Aural haematoma	Otic haematoma
349 Ear and labyrinth disorders	External ear disorders	Aural haematoma	Ear flap haemorrhage
350 Ear and labyrinth disorders	External ear disorders	Aural neoplasia NOS	Aural neoplasia NOS
351 Ear and labyrinth disorders	External ear disorders	External ear disorder NOS	External ear disorder NOS
352 Ear and labyrinth disorders	External ear disorders	External ear disorder NOS	Droopy ears
353 Ear and labyrinth disorders	External ear disorders	Otitis externa	Otitis externa
354 Ear and labyrinth disorders	External ear disorders	Pinnal cyanosis	Pinnal cyanosis
355 Ear and labyrinth disorders	External ear disorders	Pinnal cyanosis	Blue ear(s)
356 Ear and labyrinth disorders	External ear disorders	Pinnal haemorrhage	Pinal haemorrhage
357 Ear and labyrinth disorders	External ear disorders	Pinnal irritation	Pinal reddening
358 Ear and labyrinth disorders	External ear disorders	Pinnal irritation	Pinnal irritation
359 Ear and labyrinth disorders	External ear disorders	Pinnal necrosis	Pinnal necrosis
360 Ear and labyrinth disorders	External ear disorders	Pinnal oedema	Pinnal oedema
361 Ear and labyrinth disorders	External ear disorders	Pinnal oedema	Ear flap oedema
362 Ear and labyrinth disorders	Hearing abnormality	Deafness	Deafness

363	Ear and labyrinth disorders	Hearing abnormality	Deafness	Hearing affected
364	Ear and labyrinth disorders	Hearing abnormality	Deafness	Partial deafness
365	Ear and labyrinth disorders	Hearing abnormality	Deafness	Deafness NOS
366	Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Tumbling circling disease (see also ataxia at 'Neurological')
367	Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Equilibrium disorders (see also staggering and falling in 'Neurological')
368	Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Balance problems
369	Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Vestibular disorder NOS
370	Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Head tilt
371	Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Head shake (but see also 'Neurological')
372	Ear and labyrinth disorders	Internal ear disorders	Otitis interna	Otitis interna
373	Ear and labyrinth disorders	Middle ear disorders	Otitis media	Otitis media
374	Endocrine system disorders	Adrenal gland disorder	Adrenal gland disorder NOS	Adrenal gland disorder NOS
375	Endocrine system disorders	Adrenal gland disorder	Hyperadrenocorticism	Hyperadrenocorticism
376	Endocrine system disorders	Adrenal gland disorder	Hyperadrenocorticism	Cushings disease NOS
377	Endocrine system disorders	Adrenal gland disorder	Hyperadrenocorticism	Cushings disease - pituitary dependant
378	Endocrine system disorders	Adrenal gland disorder	Hyperadrenocorticism	Cushings disease - adrenal dependant
379	Endocrine system disorders	Adrenal gland disorder	Hypoadrenocorticism	Hypoadrenocorticism

380	Endocrine system disorders	Adrenal gland disorder	Hypoadrenocorticism	Addison's disease
381	Endocrine system disorders	Congenital endocrine disorders	Congenital endocrine disorder	Congenital endocrine disorder
382	Endocrine system disorders	Endocrine neoplasms	Endocrine neoplasm	Endocrine neoplasm
383	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Diabetes
384	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Uncontrolled diabetes
385	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Diabetes mellitus
386	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Hypoglycaemia
387	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Diabetic coma
388	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Glucose intolerance
389	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Complications of diabetes
390	Endocrine system disorders	Pancreas endocrine disorders	Diabetes mellitus	Hyperglycaemia
391	Endocrine system disorders	Pancreas endocrine disorders	Endocrine pancreatitis	Endocrine pancreatitis
392	Endocrine system disorders	Pancreas endocrine disorders	Pancreas endocrine disorder NOS	Pancreas endocrine disorder NOS

393 Endocrine system disorders	Parathyroid disorders	Hyperparathyroidism	Hyperparathyroidism
394 Endocrine system disorders	Parathyroid disorders	Hypoparathyroidism	Hypoparathyroidism
395 Endocrine system disorders	Parathyroid disorders	Parathyroid disorder NOS	Parathyroid disorder NOS
396 Endocrine system disorders	Pituitary disorders	Acromegaly	Acromegaly
397 Endocrine system disorders	Pituitary disorders	Diabetes insipidus	Diabetes insipidus
398 Endocrine system disorders	Pituitary disorders	Pituitary disorder NOS	Pituitary disorder NOS
399 Endocrine system disorders	Thyroid gland disorders	Hyperthyroidism	Hyperthyroidism
400 Endocrine system disorders	Thyroid gland disorders	Hypothyroidism	Hypothyroidism
401 Endocrine system disorders	Thyroid gland disorders	Thyroid gland disorder NOS	Thyroid gland disorder NOS
402 Eye disorders	Abnormal vision	Blindness	Blindness
403 Eye disorders	Abnormal vision	Impaired vision	Impaired vision
404 Eye disorders	Abnormal vision	Impaired vision	Sight affected
405 Eye disorders	Abnormal vision	Impaired vision	Partial blindness
406 Eye disorders	Abnormal vision	Impaired vision	Amaurosis
407 Eye disorders	Congenital eye disorders	Congenital eye disorder	Congenital eye disorder
408 Eye disorders	Corneal disorders	Corneal disorder	Corneal disorder
409 Eye disorders	Corneal disorders	Corneal oedema	Corneal oedema
410 Eye disorders	Corneal disorders	Corneal oedema	Blue eye
411 Eye disorders	Corneal disorders	Corneal ulcer	Corneal ulcer

412 Eye disorders	Corneal disorders	Keratitis	Keratitis
413 Eye disorders	Eye-chamber (anterior and posterior) disorders	Glaucoma	Glaucoma
414 Eye disorders	Eye-chamber (anterior and posterior) disorders	Hyphaemia	Hyphaemia
415 Eye disorders	Eye-chamber (anterior and posterior) disorders	Hypopyon	Hypopyon
416 Eye disorders	Eyelid disorders	Blepharitis	Palpebral oedema
417 Eye disorders	Eyelid disorders	Blepharitis	Blepharitis
418 Eye disorders	Eyelid disorders	Blepharitis	Eyelid inflammation
419 Eye disorders	Eyelid disorders	Blepharospasm	Blepharospasm
420 Eye disorders	Eyelid disorders	Ectropion	Ectropion
421 Eye disorders	Eyelid disorders	Entropion	Entropion
422 Eye disorders	Eyelid disorders	Palpebral disorder NOS	Palpebral disorder
423 Eye disorders	Iris, ciliary body and choroid disorders	Ciliary body and choroid disorder NOS	Ciliary body and choroid disorder NOS
424 Eye disorders	Iris, ciliary body and choroid disorders	Iris disorder	Iris disorder NOS
425 Eye disorders	Iris, ciliary body and choroid disorders	Iris disorder	Iris tear
426 Eye disorders	Iris, ciliary body and choroid disorders	Iris disorder	Iris prolapse

427 Eye disorders	Iris, ciliary body and choroid disorders	Pupil disorder	Fixed pupil
428 Eye disorders	Iris, ciliary body and choroid disorders	Pupil disorder	Pupil disorder
429 Eye disorders	Iris, ciliary body and choroid disorders	Uveitis	Anterior uveitis
430 Eye disorders	Iris, ciliary body and choroid disorders	Uveitis	Posterior uveitis
431 Eye disorders	Iris, ciliary body and choroid disorders	Uveitis	Uveitis NOS
432 Eye disorders	Lacrimal gland disorders	Epiphora	Epiphora
433 Eye disorders	Lacrimal gland disorders	Epiphora	Tear flow increased
434 Eye disorders	Lacrimal gland disorders	Epiphora	Excess tear flow
435 Eye disorders	Lacrimal gland disorders	Epiphora	Lacrimation
436 Eye disorders	Lacrimal gland disorders	Epiphora	Tear flow due to blocked or infected tear ducts
437 Eye disorders	Lacrimal gland disorders	Lacrimal disorder NOS	Lacrimal disorder NOS
438 Eye disorders	Lacrimal gland disorders	Lacrimation decrease	Lacrimation decrease
439 Eye disorders	Lens disorders	Cataract	Lens opacity
440 Eye disorders	Lens disorders	Cataract	Cataract
441 Eye disorders	Lens disorders	Cataract	Cloudy eye (for Miosis, Mydriasis, Anisocoria, Nystagmus - see 'Neurological')

442 Eye disorders	Lens disorders	Lens disorder NOS	Lens disorder NOS
443 Eye disorders	Lens disorders	Lens luxation	Lens luxation
444 Eye disorders	Membrane nictitans disorders	Protrusion membrana nictitans	Protrusion membrana nictitans
445 Eye disorders	Membrane nictitans disorders	Protrusion membrana nictitans	Third eyelid extrusion
446 Eye disorders	Optic nerve disorders	Optic nerve disorder	Optic nerve disorder
447 Eye disorders	Other eye disorders	Exophthalmia	Exophthalmia
448 Eye disorders	Other eye disorders	Eye disorder NOS	Eye disorder NOS (for photophobia see 'neurological')
449 Eye disorders	Other eye disorders	Eye irritation	Eye irritation
450 Eye disorders	Other eye disorders	Eye paralysis	Eye paralysis (for Miosis etc see 'Neurological')
451 Eye disorders	Other eye disorders	Eye paralysis	Ophthalmoplegia
452 Eye disorders	Other eye disorders	Eyeball protrusion	Eyeball protrusion
453 Eye disorders	Other eye disorders	Panophthalmitis	Eye redness
454 Eye disorders	Other eye disorders	Panophthalmitis	Panophthalmitis
455 Eye disorders	Other eye disorders	Panophthalmitis	Generalised inflammation of eye
456 Eye disorders	Other eye disorders	Periorbital oedema	Periorbital oedema
457 Eye disorders	Other eye disorders	Periorbital oedema	Swelling around eye
458 Eye disorders	Retinal disorders	Retinal atrophy	Retinal atrophy
459 Eye disorders	Retinal disorders	Retinal degeneration	Retinal degeneration

460 Eye disorders	Retinal disorders	Retinal degeneration	Lack of taurine in cat
461 Eye disorders	Retinal disorders	Retinal detachment	Retinal detachment
462 Eye disorders	Retinal disorders	Retinal disorder NOS	Retinal disorder NOS
463 Eye disorders	Retinal disorders	Retinal haemorrhage	Retinal haemorrhage
464 Eye disorders	Scleral and conjunctival disorders	Conjunctivitis	Ocular discharge
465 Eye disorders	Scleral and conjunctival disorders	Conjunctivitis	Conjunctivitis
466 Eye disorders	Scleral and conjunctival disorders	Keratoconjunctivitis	Keratoconjunctivitis
467 Eye disorders	Scleral and conjunctival disorders	Keratoconjunctivitis sicca	Keratoconjunctivitis sicca
468 Eye disorders	Scleral and conjunctival disorders	Keratoconjunctivitis sicca	Dry eye
469 Eye disorders	Scleral and conjunctival disorders	Scleritis	Scleritis
470 Eye disorders	Scleral and conjunctival disorders	Scleritis	Sclerotitis
471 Eye disorders	Scleral and conjunctival disorders	Scleritis	Inflammation of eye coat
472 Hepato-biliary disorders	Gall bladder & bile duct disorders	Cholangiohepatitis	Cholangiohepatitis
473 Hepato-biliary disorders	Gall bladder & bile duct disorders	Cholangitis	Cholangitis

474 Hepato-biliary disorders	Gall bladder & bile duct disorders	Cholecystitis	Gall bladder inflammation
475 Hepato-biliary disorders	Gall bladder & bile duct disorders	Cholecystitis	Cholecystitis
476 Hepato-biliary disorders	Gall bladder & bile duct disorders	Gall bladder & bile duct disorder NOS	Gall bladder & bile duct disorder NOS
477 Hepato-biliary disorders	Gall bladder & bile duct disorders	Gall stone	Gall stone
478 Hepato-biliary disorders	Gall bladder & bile duct disorders	Gall stone	Cholelithiasis
479 Hepato-biliary disorders	Hepatic disorders	Fatty liver	Fatty liver
480 Hepato-biliary disorders	Hepatic disorders	Hepatic abscess	Hepatic abscess
481 Hepato-biliary disorders	Hepatic disorders	Hepatic abscess	Liver abscess
482 Hepato-biliary disorders	Hepatic disorders	Hepatic encephalopathy	Hepatic encephalopathy
483 Hepato-biliary disorders	Hepatic disorders	Hepatic fibrosis	Cirrhosis
484 Hepato-biliary disorders	Hepatic disorders	Hepatic fibrosis	Hepatic fibrosis
485 Hepato-biliary disorders	Hepatic disorders	Hepatic fibrosis	Hepatic cirrhosis
486 Hepato-biliary disorders	Hepatic disorders	Hepatic fibrosis	Liver fibrosis
487 Hepato-biliary disorders	Hepatic disorders	Hepatic necrosis	Hepatic necrosis
488 Hepato-biliary disorders	Hepatic disorders	Hepatic toxicosis	Hepatic toxicosis
489 Hepato-biliary disorders	Hepatic disorders	Hepatitis	Hepatitis

490 Hepato-biliary disorders	Hepatic disorders	Hepatomegaly	Hepatomegaly
491 Hepato-biliary disorders	Hepatic disorders	Hepatomegaly	Enlarged liver
492 Hepato-biliary disorders	Hepatic disorders	Hepatopathy	Hepatopathy
493 Hepato-biliary disorders	Hepatic disorders	Hepatopathy	Hepatic failure
494 Hepato-biliary disorders	Hepatic disorders	Hepatopathy	Hepatic insufficiency
495 Hepato-biliary disorders	Hepatic disorders	Icterus	Icterus
496 Hepato-biliary disorders	Hepatic disorders	Icterus	Yellow mucus membranes
497 Hepato-biliary disorders	Hepatic disorders	Icterus	Jaundice
498 Hepato-biliary disorders	Hepatic vascular disorders	Hepatic vascular disorder	Hepatic vascular disorder
499 Hepato-biliary disorders	Hepato-biliary congenital disorders	Hepato-biliary congenital disorder	Hepato-biliary congenital disorder
500 Hepato-biliary disorders	Hepato-biliary congenital disorders	Hepato-biliary congenital disorder	Portacaval shunt
501 Hepato-biliary disorders	Hepato-biliary neoplasms	Hepatic neoplasm	Liver tumour
502 Hepato-biliary disorders	Hepato-biliary neoplasms	Hepatic neoplasm	Hepatic tumour
503 Hepato-biliary disorders	Hepato-biliary neoplasms	Hepatic neoplasm	Hepatic neoplasm
504 Immune system disorders	Autoimmune disorders	Autoimmune disorder NOS	Autoimmune disorder NOS
505 Immune system disorders	Autoimmune disorders	Pemphigus	Pemphigus
506 Immune system disorders	Bursal disorders	Bursae fabricius degeneration	Bursae fabricius degeneration
507 Immune system disorders	Bursal disorders	Bursae fabricius inflammation	Bursae fabricius inflammation

508	Immune system disorders	Hypersensitivity	Anaphylaxis	Anaphylaxis
509	Immune system disorders	Hypersensitivity	Atopic allergy	Atopic allergy (see also 'skin')
510	Immune system disorders	Hypersensitivity	Hypersensitivity	Hypersensitivity
511	Immune system disorders	Hypersensitivity	Oedema	Angioedema
512	Immune system disorders	Hypersensitivity	Oedema	Facial swelling (see also 'Skin')
513	Immune system disorders	Hypersensitivity	Oedema	Oedema of the extremities (see also other SOCs for most applicable oedema)
514	Immune system disorders	Hypersensitivity	Urticaria	Nettle rash (see also 'Skin')
515	Immune system disorders	Hypersensitivity	Urticaria	Wheals
516	Immune system disorders	Hypersensitivity	Urticaria	Urticaria
517	Immune system disorders	Other immune system disorders	Other immune system disorder NOS	Other immune system disorder NOS
518	Immune system disorders	Other immune system disorders	Sarcoidosis	Sarcoidosis
519	Mammary gland disorders	Mammary gland disorders	Acute mastitis	Erythema of the teat
520	Mammary gland disorders	Mammary gland disorders	Acute mastitis	Acute mastitis
521	Mammary gland disorders	Mammary gland disorders	Chronic mastitis	Chronic mastitis
522	Mammary gland disorders	Mammary gland disorders	Mammary gland disorder NOS	Mammary gland disorder NOS
523	Mammary gland disorders	Mammary gland disorders	Mammary gland oedema	Mammary gland oedema
524	Mammary gland disorders	Mammary gland neoplasms	Mammary gland neoplasm NOS	Mammary gland neoplasm NOS

525 Mammary gland disorders	Mammary gland neoplasms	Mammary hyperplasia	Mammary hyperplasia
526 Mammary gland disorders	Milk production disorders	Agalactia	Agalactia
527 Mammary gland disorders	Milk production disorders	Alteration of milk quality	Residues in milk
528 Mammary gland disorders	Milk production disorders	Alteration of milk quality	Alteration of milk quality
529 Mammary gland disorders	Milk production disorders	Milk production decrease	Milk drop
530 Mammary gland disorders	Milk production disorders	Milk production decrease	Milk production decrease
531 Mammary gland disorders	Milk production disorders	Milk production increase	Milk production increase
532 Mammary gland disorders	Teat disorders	External teat disorder	External teat disorder
533 Mammary gland disorders	Teat disorders	Teat canal disorder	Teat canal disorder
534 Metabolism and nutrition disorders	Congenital metabolic disorders	Congenital metabolic disorder	Congenital metabolic disorder
535 Metabolism and nutrition disorders	Electrolyte and fluid balance disorders	Acid-base disorder	Acid-base disorder
536 Metabolism and nutrition disorders	Electrolyte and fluid balance disorders	Adipsia	Not drinking
537 Metabolism and nutrition disorders	Electrolyte and fluid balance disorders	Adipsia	Adipsia
538 Metabolism and nutrition disorders	Electrolyte and fluid balance disorders	Polydipsia	Polydipsia
539 Metabolism and nutrition disorders	Electrolyte and fluid balance disorders	Polydipsia	Excessive thirst
540 Metabolism and nutrition disorders	Electrolyte and fluid balance	Polydipsia	Drinking a lot

disorders

541	Metabolism and nutrition disorders	Food intolerance syndromes	Food intolerance syndrome	Food allergy
542	Metabolism and nutrition disorders	Food intolerance syndromes	Food intolerance syndrome	Food intolerance syndrome
543	Metabolism and nutrition disorders	Food intolerance syndromes	Food intolerance syndrome	Food allergy diarrhoea and/or constipation
544	Metabolism and nutrition disorders	Nutritional and vitamin disorders	Trace element disorder	Trace element disorder
545	Metabolism and nutrition disorders	Nutritional and vitamin disorders	Trace element disorder	Selenium deficiency
546	Metabolism and nutrition disorders	Nutritional and vitamin disorders	Vitamin disorder	Vitamin disorder
547	Metabolism and nutrition disorders	Nutritional and vitamin disorders	Vitamin disorder	Vitamin deficiency
548	Metabolism and nutrition disorders	Other metabolic disorders	Hypercalcaemia	Hypercalcaemia
549	Metabolism and nutrition disorders	Other metabolic disorders	Hypercuprosis	Copper toxicity
550	Metabolism and nutrition disorders	Other metabolic disorders	Hypercuprosis	Hypercuprosis
551	Metabolism and nutrition disorders	Other metabolic disorders	Hypermagnesaemia	Hypermagnesaemia
552	Metabolism and nutrition disorders	Other metabolic disorders	Hyperphosphataemia	Hyperphosphataemia
553	Metabolism and nutrition disorders	Other metabolic disorders	Hypocalcaemia	Eclampsia
554	Metabolism and nutrition disorders	Other metabolic disorders	Hypocalcaemia	Milk fever
555	Metabolism and nutrition disorders	Other metabolic disorders	Hypocalcaemia	Hypocalcaemia

556	Metabolism and nutrition disorders	Other metabolic disorders	Hypocupraemia	Hypocupraemia
557	Metabolism and nutrition disorders	Other metabolic disorders	Hypocupraemia	Hypocuprosis
558	Metabolism and nutrition disorders	Other metabolic disorders	Hypomagnesaemia	Staggers (grass)
559	Metabolism and nutrition disorders	Other metabolic disorders	Hypomagnesaemia	Hypomagnesaemia
560	Metabolism and nutrition disorders	Other metabolic disorders	Hypophosphataemia	Hypophosphataemia
561	Metabolism and nutrition disorders	Other metabolic disorders	Ketosis	Acetonaemia
562	Metabolism and nutrition disorders	Other metabolic disorders	Ketosis	Ketosis
563	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Joint swelling
564	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Arthritis
565	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Joint effusion
566	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Joint inflammation
567	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Joint oedema
568	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Joint stiffness
569	Musculoskeletal disorders	Bone and joint disorders	Arthritis	Polyarthritis
570	Musculoskeletal disorders	Bone and joint disorders	Arthrosis	Arthrosis
571	Musculoskeletal disorders	Bone and joint disorders	Arthrosis	Polyarthrosis
572	Musculoskeletal disorders	Bone and joint disorders	Bone and joint disorder NOS	Bone and joint disorder NOS
573	Musculoskeletal disorders	Bone and joint disorders	Bone and joint disorder NOS	Knuckling

574 Musculoskeletal disorders	Bone and joint disorders	Cartilage degeneration	Cartilage degeneration
575 Musculoskeletal disorders	Bone and joint disorders	Crystal arthropathies	Crystal arthropathies
576 Musculoskeletal disorders	Bone and joint disorders	Crystal arthropathies	Gout
577 Musculoskeletal disorders	Bone and joint disorders	Delayed fracture union	Mal union
578 Musculoskeletal disorders	Bone and joint disorders	Delayed fracture union	Delayed fracture union
579 Musculoskeletal disorders	Bone and joint disorders	Delayed fracture union	Pseudoarthrosis
580 Musculoskeletal disorders	Bone and joint disorders	Fracture	Fracture
581 Musculoskeletal disorders	Bone and joint disorders	Joint pain NOS	Joint pain NOS
582 Musculoskeletal disorders	Bone and joint disorders	Joint pain NOS	Joint ache
583 Musculoskeletal disorders	Bone and joint disorders	Joint pain NOS	Joint pain
584 Musculoskeletal disorders	Bone and joint disorders	Metaphyseal osteopathy	Metaphyseal osteopathy
585 Musculoskeletal disorders	Bone and joint disorders	Osteochondritis	Osteochondritis
586 Musculoskeletal disorders	Bone and joint disorders	Osteochondritis	Osteochondritis dissecans
587 Musculoskeletal disorders	Bone and joint disorders	Osteomyelitis	Osteomyelitis
588 Musculoskeletal disorders	Bone and joint disorders	Subchondrial bone cysts	Subchondrial bone cysts
589 Musculoskeletal disorders	Bone and joint disorders	Torticollis	Torticollis
590 Musculoskeletal disorders	Bone and joint disorders	Torticollis	Wry neck
591 Musculoskeletal disorders	Bone and joint disorders	Torticollis	Lateral neck deviation
592 Musculoskeletal disorders	Congenital musculo-skeletal	Congenital musculo-skeletal disorder	Congenital musculo-skeletal disorder

	disorders		
593 Musculoskeletal disorders	Connective tissue disorders NOS	Connective tissue disorder NOS	Connective tissue disorder NOS
594 Musculoskeletal disorders	Intervertebral disc disorders	Discus prolapse	Discus prolapse
595 Musculoskeletal disorders	Jaw disorders	Jaw disorders	Jaw disorders
596 Musculoskeletal disorders	Metabolic bone disease	Osteodystrophia	Osteodystrophia
597 Musculoskeletal disorders	Metabolic bone disease	Osteodystrophia	Rubber beak/jaw
598 Musculoskeletal disorders	Metabolic bone disease	Osteomalacia	Osteomalacia
599 Musculoskeletal disorders	Muscular disorders	Equine myoglobinuria	Equine myoglobinuria
600 Musculoskeletal disorders	Muscular disorders	Equine myoglobinuria	Azoturia
601 Musculoskeletal disorders	Muscular disorders	Muscle ischaemia	Muscle anaemia
602 Musculoskeletal disorders	Muscular disorders	Muscle ischaemia	Muscle ischaemia
603 Musculoskeletal disorders	Muscular disorders	Muscle pain	Muscle pain
604 Musculoskeletal disorders	Muscular disorders	Muscle stiffness	Muscle stiffness
605 Musculoskeletal disorders	Muscular disorders	Myopathy	Myopathy
606 Musculoskeletal disorders	Muscular disorders	Myopathy	Muscle wasting
607 Musculoskeletal disorders	Muscular disorders	Myositis	Myositis
608 Musculoskeletal disorders	Muscular disorders	Myositis	Muscular inflammation
609 Musculoskeletal disorders	Musculoskeletal disorders	Hyperextension	Hyperextension

610 Musculoskeletal disorders	Musculoskeletal disorders	Lameness	Lameness
611 Musculoskeletal disorders	Musculoskeletal disorders	Laminitis	Founder
612 Musculoskeletal disorders	Musculoskeletal disorders	Laminitis	Laminitis
613 Musculoskeletal disorders	Musculoskeletal neoplasms	Chondrosarcoma	Chondrosarcoma
614 Musculoskeletal disorders	Musculoskeletal neoplasms	Osteosarcoma	Osteosarcoma
615 Musculoskeletal disorders	Musculoskeletal neoplasms	Rhabdomyosarcoma	Rhabdomyosarcoma
616 Musculoskeletal disorders	Synovial and bursa disorders	Bursitis	Bursitis
617 Musculoskeletal disorders	Synovial and bursa disorders	Synovitis	Windgalls
618 Musculoskeletal disorders	Synovial and bursa disorders	Synovitis	Synovitis
619 Musculoskeletal disorders	Synovial and bursa disorders	Synovitis	Windpuffs
620 Musculoskeletal disorders	Tendon disorders	Tendinitis	Tendinitis
621 Musculoskeletal disorders	Tendon disorders	Tendon injury	Tendon injury
622 Musculoskeletal disorders	Tendon disorders	Tendon rupture	Tendon rupture
623 Neurological disorders	Central nervous system disorders	Central nervous system depression	Central nervous system depression
624 Neurological disorders	Central nervous system disorders	Central nervous system disorder	Brain damage NOS
625 Neurological disorders	Central nervous system disorders	Central nervous system disorder	Neurological signs NOS
626 Neurological disorders	Central nervous system disorders	Central nervous system disorder	Central nervous system disorders NOS

627 Neurological disorders	Central nervous system disorders	Central nervous system infection and inflammation	Central nervous system infection and inflammation
628 Neurological disorders	Central nervous system disorders	Encephalitis	Encephalitis
629 Neurological disorders	Central nervous system disorders	Increased intracranial pressure	Increased intracranial pressure
630 Neurological disorders	Central nervous system disorders	Increased intracranial pressure	Cerebral oedema
631 Neurological disorders	Central nervous system disorders	Increased intracranial pressure	Head pressing
632 Neurological disorders	Central nervous system disorders	Meningitis	Meningitis
633 Neurological disorders	Central nervous system vascular disorders	Cerebral vascular accident	Cerebral vascular accident
634 Neurological disorders	Central nervous system vascular disorders	Cerebral vascular accident	Stroke
635 Neurological disorders	Congenital neurological disorders	Congenital neurological disorder NOS	Congenital neurological disorder NOS
636 Neurological disorders	Congenital neurological disorders	Hydrocephalus	Hydrocephalus
637 Neurological disorders	Convulsions and epilepsy	Convulsions	Convulsions
638 Neurological disorders	Convulsions and epilepsy	Convulsions	Fit
639 Neurological disorders	Convulsions and epilepsy	Convulsions	Opisthotonus
640 Neurological disorders	Convulsions and epilepsy	Convulsions	Seizure NOS

641 Neurological disorders	Convulsions and epilepsy	Convulsions	Tonic /clonic seizures
642 Neurological disorders	Convulsions and epilepsy	Epileptic seizure	Epilepsy
643 Neurological disorders	Convulsions and epilepsy	Epileptic seizure	Epileptic seizure
644 Neurological disorders	Convulsions and epilepsy	Myoclonus	Rigidity
645 Neurological disorders	Convulsions and epilepsy	Myoclonus	Myoclonus
646 Neurological disorders	Coordination & balance signs	Ataxia	Falling
647 Neurological disorders	Coordination & balance signs	Ataxia	Circling
648 Neurological disorders	Coordination & balance signs	Ataxia	Unable to stand
649 Neurological disorders	Coordination & balance signs	Ataxia	Ataxia
650 Neurological disorders	Coordination & balance signs	Ataxia	Staggering
651 Neurological disorders	Coordination & balance signs	Ataxia	Inco-ordination (see also 'Ear' - vestibular disorders)
652 Neurological disorders	Coordination & balance signs	Ataxia	Stumbling gait
653 Neurological disorders	Coordination & balance signs	Ataxia	Recumbency
654 Neurological disorders	Coordination & balance signs	Disorientation	Confusion
655 Neurological disorders	Coordination & balance signs	Disorientation	Disorientation
656 Neurological disorders	Coordination & balance signs	Hypermetria	High leg gait
657 Neurological disorders	Coordination & balance signs	Hypermetria	Hypermetria
658 Neurological disorders	Coordination & balance signs	Hypermetria	Goose stepping

659 Neurological disorders	Encephalopathies and impaired consciousness	Coma	Coma
660 Neurological disorders	Encephalopathies and impaired consciousness	Coma	Vegetative state
661 Neurological disorders	Encephalopathies and impaired consciousness	Encephalopathy NOS	Encephalopathy NOS
662 Neurological disorders	Encephalopathies and impaired consciousness	Lack of consciousness	Lack of consciousness
663 Neurological disorders	Encephalopathies and impaired consciousness	Lack of consciousness	Collapse
664 Neurological disorders	Nervous system neoplasms	Nervous system neoplasm	Nervous system neoplasm
665 Neurological disorders	Neuromuscular disorders	Anisocoria	Anisocoria
666 Neurological disorders	Neuromuscular disorders	Anisocoria	Unequal pupils
667 Neurological disorders	Neuromuscular disorders	Cholinergic disorder	Organophosphate toxicity
668 Neurological disorders	Neuromuscular disorders	Cholinergic disorder	Cholinergic disorder
669 Neurological disorders	Neuromuscular disorders	Depressed reflexes	Slow reflexes
670 Neurological disorders	Neuromuscular disorders	Depressed reflexes	Dull reflexes
671 Neurological disorders	Neuromuscular disorders	Depressed reflexes	Reduced reflexes
672 Neurological disorders	Neuromuscular disorders	Depressed reflexes	Depressed reflexes
673 Neurological disorders	Neuromuscular disorders	Hyperreflexia	Hyperreflexia
674 Neurological disorders	Neuromuscular disorders	Miosis	Reduced pupils

675 Neurological disorders	Neuromuscular disorders	Miosis	Miosis
676 Neurological disorders	Neuromuscular disorders	Muscle tremor	Spasm
677 Neurological disorders	Neuromuscular disorders	Muscle tremor	Muscle spasm NOS
678 Neurological disorders	Neuromuscular disorders	Muscle tremor	Chorea
679 Neurological disorders	Neuromuscular disorders	Muscle tremor	Muscle tremor
680 Neurological disorders	Neuromuscular disorders	Muscle tremor	Tics
681 Neurological disorders	Neuromuscular disorders	Muscle tremor	Twitching
682 Neurological disorders	Neuromuscular disorders	Muscle tremor	Trembling
683 Neurological disorders	Neuromuscular disorders	Muscle tremor	Fasciculation
684 Neurological disorders	Neuromuscular disorders	Mydriasis	Enlarged pupils
685 Neurological disorders	Neuromuscular disorders	Mydriasis	Mydriasis
686 Neurological disorders	Neuromuscular disorders	Nystagmus	Nystagmus
687 Neurological disorders	Paralytic and paretic disorders	Paralysis	Paraplegia
688 Neurological disorders	Paralytic and paretic disorders	Paralysis	Hemiplegia
689 Neurological disorders	Paralytic and paretic disorders	Paralysis	Quadriplegia
690 Neurological disorders	Paralytic and paretic disorders	Paralysis	Flaccid paralysis
691 Neurological disorders	Paralytic and paretic	Paralysis	Paralysis NOS

	disorders			
692 Neurological disorders	Paralytic and paretic disorders	Paresis		Hemiparesis
693 Neurological disorders	Paralytic and paretic disorders	Paresis		Paresis NOS
694 Neurological disorders	Paralytic and paretic disorders	Paresis		Paraparesis
695 Neurological disorders	Paralytic and paretic disorders	Paresis		Quadriparesis
696 Neurological disorders	Paralytic and paretic disorders	Spasticity		Spasticity
697 Neurological disorders	Peripheral neuropathies & neuritis	Horners syndrome		Horners syndrome
698 Neurological disorders	Sensory abnormalities	Hyperaesthesia		Hypersensitivity to pain
699 Neurological disorders	Sensory abnormalities	Hyperaesthesia		Photophobia
700 Neurological disorders	Sensory abnormalities	Hyperaesthesia		Hypersensitivity to light
701 Neurological disorders	Sensory abnormalities	Hyperaesthesia		Hyperaesthesia
702 Neurological disorders	Sensory abnormalities	Hyperaesthesia		Hypersensitivity to movement
703 Neurological disorders	Spinal cord & spinal nerve root disorders	Cervical spondylopathy		Cervical spondylopathy
704 Neurological disorders	Spinal cord & spinal nerve root disorders	Cervical spondylopathy		Wobbler
705 Renal and urinary disorders	Congenital renal and urinary	Congenital renal and urinary tract		Congenital renal and urinary tract

	tract disorders	disorder NOS	disorder NOS
706 Renal and urinary disorders	Renal disorders	Anuria	Oliguria
707 Renal and urinary disorders	Renal disorders	Anuria	Anuria
708 Renal and urinary disorders	Renal disorders	Nephritis	Glomerulonephritis
709 Renal and urinary disorders	Renal disorders	Nephritis	Nephritis NOS
710 Renal and urinary disorders	Renal disorders	Nephritis	Interstitial nephritis
711 Renal and urinary disorders	Renal disorders	Nephritis	Pyelonephritis
712 Renal and urinary disorders	Renal disorders	Nephropathy	Nephropathy
713 Renal and urinary disorders	Renal disorders	Polyuria	Polyuria
714 Renal and urinary disorders	Renal disorders	Renal disorder NOS	Renal disorder NOS
715 Renal and urinary disorders	Renal disorders	Renal failure	Renal failure
716 Renal and urinary disorders	Renal disorders	Renal insufficiency	Renal insufficiency
717 Renal and urinary disorders	Renal disorders	Renal insufficiency	Uraemia
718 Renal and urinary disorders	Renal disorders	Renal vascular disorder	Renal vascular disorder
719 Renal and urinary disorders	Ureteric disorders	Ureteric disorder	Ureteric disorder
720 Renal and urinary disorders	Urinary bladder disorders	Cystitis	Cystitis
721 Renal and urinary disorders	Urinary bladder disorders	Dysuria	Urinary tenesmus
722 Renal and urinary disorders	Urinary bladder disorders	Dysuria	Dysuria
723 Renal and urinary disorders	Urinary bladder disorders	Haematuria	Urinary tract bleeding

724 Renal and urinary disorders	Urinary bladder disorders	Haematuria	Haematuria
725 Renal and urinary disorders	Urinary bladder disorders	Haematuria	Haemorrhagic bladder
726 Renal and urinary disorders	Urinary bladder disorders	Pungent urine	Pungent urine
727 Renal and urinary disorders	Urinary bladder disorders	Urinary bladder disorder NOS	Urinary bladder disorder NOS
728 Renal and urinary disorders	Urinary bladder disorders	Urinary incontinence	Frequent urination
729 Renal and urinary disorders	Urinary bladder disorders	Urinary incontinence	Frequent micturition
730 Renal and urinary disorders	Urinary bladder disorders	Urinary incontinence	Urinary incontinence
731 Renal and urinary disorders	Urinary bladder disorders	Urinary incontinence	Uncontrolled micturition
732 Renal and urinary disorders	Urinary bladder disorders	Urinary retention	Urinary retention
733 Renal and urinary disorders	Urinary tract disorders	Stranguria	Stranguria
734 Renal and urinary disorders	Urinary tract disorders	Urinary tract disorder NOS	Urinary tract disorder NOS
735 Renal and urinary disorders	Urinary tract disorders	Urolithiasis	Urolithiasis
736 Renal and urinary disorders	Urinary tract disorders	Urolithiasis	Calculi
737 Renal and urinary disorders	Urinary tract neoplasms	Urinary tract neoplasm	Urinary tract neoplasm
738 Reproductive system disorders	Avian reproductive system disorders	Egg drop	Egg drop
739 Reproductive system disorders	Avian reproductive system disorders	Egg drop	Loss of egg quality
740 Reproductive system disorders	Avian reproductive system disorders	Egg drop	Loss of egg quantity

741	Reproductive system disorders	Avian reproductive system disorders	Egg drop	Reduced hatchability
742	Reproductive system disorders	Avian reproductive system disorders	Egg drop	Egg drop syndrome
743	Reproductive system disorders	Avian reproductive system disorders	Egg peritonitis	Egg peritonitis
744	Reproductive system disorders	Cervix disorders	Cervix disorder	Abnormal cervix
745	Reproductive system disorders	Cervix disorders	Cervix disorder	Failure to dilate
746	Reproductive system disorders	Cervix disorders	Cervix disorder	Cervix disorder NOS
747	Reproductive system disorders	Congenital reproductive tract disorders	Congenital reproductive tract disorder	Freemartin
748	Reproductive system disorders	Congenital reproductive tract disorders	Congenital reproductive tract disorder	Congenital reproductive tract disorder NOS
749	Reproductive system disorders	Cryptorchidism	Cryptorchidism	Cryptorchidism
750	Reproductive system disorders	Cryptorchidism	Cryptorchidism	Cryptorchidy
751	Reproductive system disorders	Disorders of oestral cycle	Anoestrus	Anoestrus
752	Reproductive system disorders	Disorders of oestral cycle	Anoestrus	Lack of heat
753	Reproductive system disorders	Disorders of oestral cycle	Polyoestrus	Polyoestrus
754	Reproductive system disorders	Disorders of oestral cycle	Polyoestrus	Continuous heat
755	Reproductive system disorders	Disorders of oestral cycle	Suboestrus	Quiet heat
756	Reproductive system disorders	Female reproductive tract neoplasms	Female reproductive tract neoplasm NOS	Female reproductive tract neoplasm NOS

757	Reproductive system disorders	Fertility disorders	Abnormal spermatazoa	Abnormal spermatazoa
758	Reproductive system disorders	Fertility disorders	Infertility NOS	Infertility NOS
759	Reproductive system disorders	Gonadotrophin and sex hormone changes	Nymphomania	Nymphomania
760	Reproductive system disorders	Gonadotrophin and sex hormone changes	Pseudopregnancy	Pseudopregnancy
761	Reproductive system disorders	Male reproductive tract disorders	Male reproductive tract disorder NOS	Male reproductive tract disorder NOS
762	Reproductive system disorders	Male reproductive tract neoplasms	Male reproductive tract neoplasm NOS	Male reproductive tract neoplasm NOS
763	Reproductive system disorders	Other female reproductive tract disorders	Female reproductive tract disorder NOS	Female reproductive tract disorder NOS
764	Reproductive system disorders	Ovarian disorders	Luteolysis	Luteolysis
765	Reproductive system disorders	Ovarian disorders	Ovarian cysts	Ovarian cysts
766	Reproductive system disorders	Oviduct disorders	Impaction of oviduct	Impaction of oviduct
767	Reproductive system disorders	Oviduct disorders	Oviduct cysts	Oviduct cysts
768	Reproductive system disorders	Oviduct disorders	Salpingitis	Salpingitis
769	Reproductive system disorders	Pregnancy and parturition	Abortion	Abortion
770	Reproductive system disorders	Pregnancy and parturition	Birth defect	Birth defect
771	Reproductive system disorders	Pregnancy and parturition	Dystocia	Dystocia
772	Reproductive system disorders	Pregnancy and parturition	Foetal maceration	Foetal maceration

773 Reproductive system disorders	Pregnancy and parturition	Foetal mummification	Foetal mummification
774 Reproductive system disorders	Pregnancy and parturition	Foetal reabsorption	Return to oestrus
775 Reproductive system disorders	Pregnancy and parturition	Foetal reabsorption	Foetal reabsorption
776 Reproductive system disorders	Pregnancy and parturition	Perinatal mortality	Perinatal mortality
777 Reproductive system disorders	Pregnancy and parturition	Perinatal mortality NOS	Perinatal mortality NOS
778 Reproductive system disorders	Pregnancy and parturition	Placental abnormalities	Placental abnormalities
779 Reproductive system disorders	Pregnancy and parturition	Pregnancy	Pregnancy
780 Reproductive system disorders	Pregnancy and parturition	Premature parturition	Premature birth
781 Reproductive system disorders	Pregnancy and parturition	Premature parturition	Premature parturition
782 Reproductive system disorders	Pregnancy and parturition	Retained placenta	Retained placenta
783 Reproductive system disorders	Pregnancy and parturition	Retained placenta	Retained foetal membranes
784 Reproductive system disorders	Pregnancy and parturition	Runt	Runt
785 Reproductive system disorders	Pregnancy and parturition	Stillbirth	Stillbirth
786 Reproductive system disorders	Pregnancy and parturition	Stillbirth	Intrauterine death
787 Reproductive system disorders	Prostatic disorders	Prostate hyperplasia	Prostate hyperplasia
788 Reproductive system disorders	Prostatic disorders	Prostatic tumour	Prostatic tumour
789 Reproductive system disorders	Scrotal and penile disorders	Balanoposthitis	Balanoposthitis
790 Reproductive system disorders	Scrotal and penile disorders	Penile disorder NOS	Penile disorder NOS
791 Reproductive system disorders	Scrotal and penile disorders	Phimosis	Paraphimosis

792 Reproductive system disorders	Scrotal and penile disorders	Phimosis	Phimosis
793 Reproductive system disorders	Scrotal and penile disorders	Preputial discharge	Preputial discharge
794 Reproductive system disorders	Scrotal and penile disorders	Preputial prolapse	Preputial prolapse
795 Reproductive system disorders	Scrotal and penile disorders	Priapism	Priapism
796 Reproductive system disorders	Scrotal and penile disorders	Scrotal disorder NOS	Scrotal disorder NOS
797 Reproductive system disorders	Scrotal and penile disorders	Scrotitis	Scrotitis
798 Reproductive system disorders	Scrotal and penile disorders	Scrotitis	Scrotal oedema
799 Reproductive system disorders	Testicular and epididymal disorders	Epididymitis	Epididymitis
800 Reproductive system disorders	Testicular and epididymal disorders	Orchitis	Orchitis
801 Reproductive system disorders	Uterine disorders	Metritis	Endometritis
802 Reproductive system disorders	Uterine disorders	Metritis	Mucometra
803 Reproductive system disorders	Uterine disorders	Metritis	Stump pyometra
804 Reproductive system disorders	Uterine disorders	Metritis	Delayed uterine involution
805 Reproductive system disorders	Uterine disorders	Metritis	Pyometra
806 Reproductive system disorders	Uterine disorders	Uterine haemorrhage	Uterine haemorrhage
807 Reproductive system disorders	Uterine disorders	Uterine prolapse	Uterine prolapse
808 Reproductive system disorders	Uterine disorders	Uterine rupture	Uterine rupture
809 Reproductive system disorders	Uterine disorders	Uterine torsion	Uterine torsion

810 Reproductive system disorders	Vulvovaginal disorders	Vaginal haemorrhage	Vaginal haemorrhage
811 Reproductive system disorders	Vulvovaginal disorders	Vaginal hyperplasia	Vaginal hyperplasia
812 Reproductive system disorders	Vulvovaginal disorders	Vaginal prolapse	Vaginal prolapse
813 Reproductive system disorders	Vulvovaginal disorders	Vaginal tear	Vaginal tear
814 Reproductive system disorders	Vulvovaginal disorders	Vaginal vesicles	Vaginal vesicles
815 Reproductive system disorders	Vulvovaginal disorders	Vulvovaginitis	Vaginitis
816 Reproductive system disorders	Vulvovaginal disorders	Vulvovaginitis	Vulvitis
817 Reproductive system disorders	Vulvovaginal disorders	Vulvovaginitis	Vulvovaginitis
818 Reproductive system disorders	Vulvovaginal disorders	Vulvovaginitis	Swollen vulva
819 Reproductive system disorders	Vulvovaginal disorders	Vulvovaginitis	Vaginal oedema
820 Reproductive system disorders	Vulvovaginal disorders	Vulvovaginitis	Vaginal swelling
821 Respiratory tract disorders	Avian respiratory disorders	Airsacculitis	Airsacculitis
822 Respiratory tract disorders	Bronchial & lung disorders	Anoxia	Anoxia
823 Respiratory tract disorders	Bronchial & lung disorders	Apnoea	Apnoea
824 Respiratory tract disorders	Bronchial & lung disorders	Apnoea	Respiratory arrest
825 Respiratory tract disorders	Bronchial & lung disorders	Asthma	Asthma
826 Respiratory tract disorders	Bronchial & lung disorders	Bradypnoea	Bradypnoea
827 Respiratory tract disorders	Bronchial & lung disorders	Bradypnoea	Decreased respiratory rate
828 Respiratory tract disorders	Bronchial & lung disorders	Bronchitis	Bronchitis

829 Respiratory tract disorders	Bronchial & lung disorders	Bronchitis	Wheezing
830 Respiratory tract disorders	Bronchial & lung disorders	Dyspnoea	Abnormal breathing
831 Respiratory tract disorders	Bronchial & lung disorders	Dyspnoea	Irregular breathing
832 Respiratory tract disorders	Bronchial & lung disorders	Dyspnoea	Dyspnoea
833 Respiratory tract disorders	Bronchial & lung disorders	Dyspnoea	Respiratory distress
834 Respiratory tract disorders	Bronchial & lung disorders	Dyspnoea	Cheyne-Stokes respiration
835 Respiratory tract disorders	Bronchial & lung disorders	Pneumonia	Pneumonia
836 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary congestion	Pulmonary congestion
837 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary disorder NOS	Pulmonary disorder NOS
838 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary emphysema	Pulmonary emphysema
839 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary haemorrhage	Haemoptysis
840 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary haemorrhage	Pulmonary haemorrhage
841 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary oedema	Pulmonary oedema
842 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary oedema	Lung oedema
843 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary oedema	Bronchial oedema
844 Respiratory tract disorders	Bronchial & lung disorders	Pulmonary thromboembolism	Pulmonary thromboembolism
845 Respiratory tract disorders	Bronchial & lung disorders	Rales	Rales
846 Respiratory tract disorders	Bronchial & lung disorders	Rales	Rattling chest
847 Respiratory tract disorders	Bronchial & lung disorders	Tachypnoea	Tachypnoea

848 Respiratory tract disorders	Bronchial & lung disorders	Tachypnoea	Panting
849 Respiratory tract disorders	Bronchial & lung disorders	Tachypnoea	Increased respiratory rate
850 Respiratory tract disorders	Bronchial & lung disorders	Tachypnoea	Polypnoea
851 Respiratory tract disorders	Congenital respiratory tract disorders	Congenital respiratory tract disorder NOS	Congenital respiratory tract disorder NOS
852 Respiratory tract disorders	Congenital respiratory tract disorders	Hypoplastic trachea	Hypoplastic trachea
853 Respiratory tract disorders	Fish respiratory disorder	Fish asphyxia	Fish asphyxia
854 Respiratory tract disorders	Fish respiratory disorder	Fish asphyxia	Fish gasping
855 Respiratory tract disorders	Fish respiratory disorder	Inflammation of gills	Inflammation of gills
856 Respiratory tract disorders	Nasal cavity and sinus disorders	Epistaxis	Nasal bleeding
857 Respiratory tract disorders	Nasal cavity and sinus disorders	Epistaxis	Epistaxis
858 Respiratory tract disorders	Nasal cavity and sinus disorders	Nasal cavity and sinus disorder NOS	Nasal cavity and sinus disorder NOS
859 Respiratory tract disorders	Nasal cavity and sinus disorders	Rhinitis	Purulent rhinitis
860 Respiratory tract disorders	Nasal cavity and sinus disorders	Rhinitis	Snuffles
861 Respiratory tract disorders	Nasal cavity and sinus disorders	Rhinitis	Rhinitis NOS
862 Respiratory tract disorders	Nasal cavity and sinus	Rhinitis	Rhinitis

	disorders		
863 Respiratory tract disorders	Nasal cavity and sinus disorders	Rhinitis	Sniffing
864 Respiratory tract disorders	Nasal cavity and sinus disorders	Rhinitis	Nasal discharge
865 Respiratory tract disorders	Nasal cavity and sinus disorders	Sinusitis	Sinusitis
866 Respiratory tract disorders	Nasal cavity and sinus disorders	Sneezing	Sneezing
867 Respiratory tract disorders	Neonatal respiratory tract disorders	Neonatal respiratory disorder	Neonatal respiratory disorder
868 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Foam in the trachea	Foam in the trachea
869 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Laryngitis	Laryngitis
870 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Tracheal bleeding	Tracheal bleeding
871 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Tracheal bleeding	Blood in trachea
872 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Tracheal collapse	Tracheal collapse
873 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Tracheal obstruction	Tracheal obstruction
874 Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Tracheitis	Mucus in trachea

875	Respiratory tract disorders	Pharyngeal, tracheal and laryngeal disorders	Tracheitis	Tracheitis
876	Respiratory tract disorders	Respiratory tract disorders	Cough	Obstructive airway cough
877	Respiratory tract disorders	Respiratory tract disorders	Cough	Cough
878	Respiratory tract disorders	Respiratory tract disorders	Cough	Cough NOS
879	Respiratory tract disorders	Respiratory tract disorders	Cough	Upper respiratory tract cough
880	Respiratory tract disorders	Respiratory tract disorders	Cough	Lower respiratory tract cough
881	Respiratory tract disorders	Respiratory tract neoplasms	Respiratory tract neoplasm NOS	Respiratory tract neoplasm NOS
882	Respiratory tract disorders	Thoracic cavity disorders	Haemothorax	Haemothorax
883	Respiratory tract disorders	Thoracic cavity disorders	Hydrothorax	Hydrothorax
884	Respiratory tract disorders	Thoracic cavity disorders	Pleuritis	Pleural inflammation
885	Respiratory tract disorders	Thoracic cavity disorders	Pleuritis	Pleuritis
886	Respiratory tract disorders	Thoracic cavity disorders	Pyothorax	Pyothorax
887	Skin and integument disorders	Congenital skin disorders	Congenital skin disorder NOS	Congenital skin disorder NOS
888	Skin and integument disorders	Cornification and elastic tissue disorders	Cornification and elastic tissue disorder NOS	Cornification and elastic tissue disorder NOS
889	Skin and integument disorders	Cornification and elastic tissue disorders	Hyperkeratosis	Hyperkeratosis
890	Skin and integument disorders	Fish skin disorders	Fish skin disorder	Fish skin disorder
891	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Alopecia general	Alopecia general

892	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Alopecia general	General hair loss
893	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Alopecia local	Alopecia local
894	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Alopecia local	Localised hair loss
895	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Anhidrosis	Anhidrosis
896	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Dry Coat	Staring coat
897	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Folliculitis	Folliculitis
898	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Folliculitis	Acne
899	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Furunculosis	Furunculosis
900	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Hair modification NOS	Hair modification NOS
901	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Malodour	Malodour
902	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Piloerection	Hair standing on end
903	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Piloerection	Piloerection
904	Skin and integument disorders	Hair follicle and sebaceous	Seborrhoea	Seborrhoea

	gland disorders		
905	Skin and integument disorders	Hair follicle and sebaceous gland disorders	Seborrhoea Greasy skin
906	Skin and integument disorders	Pigmentation disorders	Hyperpigmentation Hyperpigmentation
907	Skin and integument disorders	Pigmentation disorders	Hyperpigmentation Melanosis
908	Skin and integument disorders	Pigmentation disorders	Hypopigmentation Hypopigmentation
909	Skin and integument disorders	Skin and integument neoplasms	Fibrosarcoma Fibrosarcoma
910	Skin and integument disorders	Skin and integument neoplasms	Histiocytoma Histiocytoma
911	Skin and integument disorders	Skin and integument neoplasms	Melanoma Melanoma
912	Skin and integument disorders	Skin and integument neoplasms	Myofibrosarcoma Myofibrosarcoma
913	Skin and integument disorders	Skin and integument neoplasms	Papilloma Papilloma
914	Skin and integument disorders	Skin and integument neoplasms	Skin and integument neoplasm NOS Skin sarcoma NOS
915	Skin and integument disorders	Skin and integument neoplasms	Skin and integument neoplasm NOS Skin and integument neoplasms NOS
916	Skin and integument disorders	Skin and integument neoplasms	Skin and integument neoplasm NOS Skin tumour NOS
917	Skin and integument disorders	Skin and integument neoplasms	Spindle cell tumour Spindle cell tumour

918	Skin and integument disorders	Skin disorders	Bullae	Bullae
919	Skin and integument disorders	Skin disorders	Burn	Caustic burn
920	Skin and integument disorders	Skin disorders	Burn	Chemical burn
921	Skin and integument disorders	Skin disorders	Dermal cysts	Dermal cysts
922	Skin and integument disorders	Skin disorders	Dermal thickening	Dermal thickening
923	Skin and integument disorders	Skin disorders	Dermatitis	Moist eczema
924	Skin and integument disorders	Skin disorders	Dermatitis	Dermatitis NOS
925	Skin and integument disorders	Skin disorders	Dermatitis	Scaling
926	Skin and integument disorders	Skin disorders	Dermatitis	Eczema
927	Skin and integument disorders	Skin disorders	Dermatitis	Pimples
928	Skin and integument disorders	Skin disorders	Dermatitis	Ulcerative dermatitis
929	Skin and integument disorders	Skin disorders	Dermatitis	Moist dermatitis
930	Skin and integument disorders	Skin disorders	Dermatitis	Pustules
931	Skin and integument disorders	Skin disorders	Dermatitis	Rash
932	Skin and integument disorders	Skin disorders	Dermatomycosis	Dermatomycosis
933	Skin and integument disorders	Skin disorders	Dermatosis NOS	Dermatosis NOS
934	Skin and integument disorders	Skin disorders	Desquamation	Desquamation
935	Skin and integument disorders	Skin disorders	Desquamation	Skin slough
936	Skin and integument disorders	Skin disorders	Desquamation	Peeling skin

937	Skin and integument disorders	Skin disorders	Erosion	Erosion
938	Skin and integument disorders	Skin disorders	Erythema	Reddening of the skin
939	Skin and integument disorders	Skin disorders	Erythema	Rubra
940	Skin and integument disorders	Skin disorders	Erythema	Erythema
941	Skin and integument disorders	Skin disorders	Erythema	Skin hyperaemia
942	Skin and integument disorders	Skin disorders	Granuloma	Granuloma
943	Skin and integument disorders	Skin disorders	Panniculitis	Panniculitis
944	Skin and integument disorders	Skin disorders	Papillomatosis	Papillomatosis
945	Skin and integument disorders	Skin disorders	Papule	Papule
946	Skin and integument disorders	Skin disorders	Petechiation	Petechiation
947	Skin and integument disorders	Skin disorders	Photosensitivity	Photosensitivity
948	Skin and integument disorders	Skin disorders	Photosensitivity	Photosensitization
949	Skin and integument disorders	Skin disorders	Photosensitivity	Sunburn
950	Skin and integument disorders	Skin disorders	Pruritus	Itching
951	Skin and integument disorders	Skin disorders	Pruritus	Scratching
952	Skin and integument disorders	Skin disorders	Pruritus	Pruritus
953	Skin and integument disorders	Skin disorders	Pyoderma	Pyoderma
954	Skin and integument disorders	Skin disorders	Pyoderma	Sores
955	Skin and integument disorders	Skin disorders	Self trauma	Self trauma

956 Skin and integument disorders	Skin disorders	Seroma	Seroma
957 Skin and integument disorders	Skin disorders	Skin abscess NOS	Skin abscess NOS
958 Skin and integument disorders	Skin disorders	Skin haematoma	Skin haematoma
959 Skin and integument disorders	Skin disorders	Skin lesion NOS	Skin lesion NOS
960 Skin and integument disorders	Skin disorders	Skin necrosis	Skin necrosis
961 Skin and integument disorders	Skin disorders	Skin oedema	Skin oedema
962 Skin and integument disorders	Skin disorders	Skin oedema	Skin swelling
963 Skin and integument disorders	Skin disorders	Skin oedema	Cellulitis
964 Skin and integument disorders	Skin disorders	Toxic epidermal necrolysis	Toxic epidermal necrolysis
965 Skin and integument disorders	Skin disorders	Vesicle	Vesicle
966 Skin and integument disorders	Skin vascular disorders	Skin vascular disorder NOS	Skin vascular disorder NOS
967 Skin and integument disorders	Sweating disorders	Hyperhidrosis	Increased sweating
968 Skin and integument disorders	Sweating disorders	Hyperhidrosis	Hyperhidrosis
969 Systemic disorders	Avian systemic disorders	Avian systemic disorder NOS	Unable to fly
970 Systemic disorders	Avian systemic disorders	Avian systemic disorder NOS	Avian general disorder NOS
971 Systemic disorders	Avian systemic disorders	Avian systemic disorder NOS	Avian systemic disorder NOS
972 Systemic disorders	Avian systemic disorders	Dropped wings	Dropped wings
973 Systemic disorders	Avian systemic disorders	Ruffled feathers	Ruffled feathers
974 Systemic disorders	Death	Death	Death by euthanasia

975 Systemic disorders	Death	Death	Sudden death
976 Systemic disorders	Death	Death	Found dead
977 Systemic disorders	Death	Death	Death
978 Systemic disorders	Death	Death	Death unexplained
979 Systemic disorders	Dwarfism	Dwarfism	Dwarfism
980 Systemic disorders	Fish systemic disorders	Fish body deformity	Fish body deformity
981 Systemic disorders	Fish systemic disorders	Fish body deformity	Fish malformation
982 Systemic disorders	Fish systemic disorders	Fish body deformity	Fish acquired dwarfism
983 Systemic disorders	Fish systemic disorders	Fish body deformity	Fish pinhead
984 Systemic disorders	Fish systemic disorders	Fish colour change	Fish colour change
985 Systemic disorders	Fish systemic disorders	Fish colour change	Fish chromatophage disorder
986 Systemic disorders	Fish systemic disorders	Fish colour change	Fish discolouration
987 Systemic disorders	Fish systemic disorders	Sinking, fish	Sinking, fish
988 Systemic disorders	Fish systemic disorders	Torpor, fish	Torpor, fish
989 Systemic disorders	General signs	Anorexia	Anorexia
990 Systemic disorders	General signs	Anorexia	Appetite loss
991 Systemic disorders	General signs	Anorexia	Decreased appetite
992 Systemic disorders	General signs	Anorexia	Inappetence
993 Systemic disorders	General signs	Collapse without loss of	Collapse without loss of

		consciousness	consciousness
994 Systemic disorders	General signs	Collapse without loss of consciousness	Collapse NOS (see also 'Neurological' and 'Cardio-vascular')
995 Systemic disorders	General signs	Congested mucous membranes	Congestion of mucous membranes
996 Systemic disorders	General signs	Congested mucous membranes	Red mucosae
997 Systemic disorders	General signs	Congested mucous membranes	Inflamed mucosae
998 Systemic disorders	General signs	Congested mucous membranes	Hyperaemic mucosae
999 Systemic disorders	General signs	Congested mucous membranes	Hyperaemic mucus membranes (see 'Cardio-vascular' for pale mucosae)
1000 Systemic disorders	General signs	Congested mucous membranes	Congested mucous membranes
1001 Systemic disorders	General signs	Congested mucous membranes	Hyperaemia
1002 Systemic disorders	General signs	Cyanosis	Cyanosis
1003 Systemic disorders	General signs	Emphysema NOS	Emphysema NOS (see 'Respiratory' for pulmonary emphysema)
1004 Systemic disorders	General signs	General pain	General pain (see other SOCs for specific pain)
1005 Systemic disorders	General signs	General pain	Pain NOS
1006 Systemic disorders	General signs	Hyperthermia	Malignant hyperthermia
1007 Systemic disorders	General signs	Hyperthermia	Hyperthermia
1008 Systemic disorders	General signs	Hypothermia	Hypothermia
1009 Systemic disorders	General signs	Hypothermia	Decreased body temperature

1010 Systemic disorders	General signs	Lethargy	Prostration
1011 Systemic disorders	General signs	Lethargy	Lethargy (see also Central nervous system depression in 'Neurological')
1012 Systemic disorders	General signs	Lethargy	Stupor
1013 Systemic disorders	General signs	Lethargy	Lack of awareness
1014 Systemic disorders	General signs	Lethargy	Reduced responses
1015 Systemic disorders	General signs	Lethargy	Listless
1016 Systemic disorders	General signs	Lethargy	Weakness
1017 Systemic disorders	General signs	Lethargy	Depression
1018 Systemic disorders	General signs	Lethargy	Reluctant to move
1019 Systemic disorders	General signs	Localised pain NOS	Localised pain NOS (see other 'SOCs' for specific pain)
1020 Systemic disorders	General signs	Malaise	Malaise
1021 Systemic disorders	General signs	Malaise	Off colour
1022 Systemic disorders	General signs	Oedema NOS	Oedema NOS (see other SOC's for specific oedemas)
1023 Systemic disorders	General signs	Oedema NOS	Ascites
1024 Systemic disorders	General signs	Pyrexia	Pyrexia
1025 Systemic disorders	General signs	Pyrexia	Fever
1026 Systemic disorders	General signs	Pyrexia	Elevated temperature

1027 Systemic disorders	General signs	Pyrexia	Febrile
1028 Systemic disorders	General signs	Septicaemia	Septicaemia
1029 Systemic disorders	General signs	Steatitis	Steatitis
1030 Systemic disorders	General signs	Steatitis	Necrotising steatitis
1031 Systemic disorders	General signs	Ulceration NOS	Ulceration NOS
1032 Systemic disorders	Lack of efficacy	Lack of efficacy	Lack of efficacy
1033 Systemic disorders	Multi-organ failure	Moribund	Moribund
1034 Systemic disorders	Multi-organ failure	Multi-organ failure NOS	Multi-organ failure NOS
1035 Systemic disorders	Performance disorders	Exercise intolerance	Exercise intolerance
1036 Systemic disorders	Performance disorders	Loss of condition	Weight loss
1037 Systemic disorders	Performance disorders	Loss of condition	Loss of condition
1038 Systemic disorders	Performance disorders	Loss of condition	Loss of condition score
1039 Systemic disorders	Performance disorders	Loss of condition	Devitalisation
1040 Systemic disorders	Performance disorders	Poor feed conversion	Poor feed conversion
1041 Systemic disorders	Performance disorders	Poor feed conversion	Low weight gain
1042 Systemic disorders	Performance disorders	Weight gain	Increased weight
1043 Systemic disorders	Performance disorders	Weight gain	Weight gain
1044 Systemic disorders	Systemic disorders NOS	Cachexia	Cachexia
1045 Systemic disorders	Systemic disorders NOS	Systemic disorder NOS	Systemic disorder NOS

**PART IV- REFERENCE LEGISLATIVE AND ADMINISTRATIVE
INFORMATION**

1. Extracts from Relevant Pharmacovigilance Legislation

EU legislation concerning human pharmacovigilance:

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (OJ L311,28.11.2001, p.67) as amended by Commission Directive 2003/63/EC of 25 June 2003 (OJ L159, 27.06.2003, p.46)

Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. (OJ L121/34, 1.5.2001)

Council Regulation (EEC) 2309/93, of 22 July 1993, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. (OJ L214,24.08.1993, p.1)

Commission Regulation (EC) 540/95, of 10 March 1995, laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in the third country, to a medicinal products for human or veterinary use authorised in accordance with the provisions of Council Regulation (EEC) No 2309/93.(OJ L55, 11.03.1995, p.5)

Commission Regulation(EC) No 1084/2003 of 3 June 2003 [ex Commission Regulation (EC) 541/95 of 10 March 1995], concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State. (OJ L159, 27.06.2003, p.1)

Commission Regulation (EC) No 1085/2003 of 3 June 2003[ex Commission Regulation (EC) 542/95 of 10 March 1995] , concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93. (OJ L159, 27.06.2003, p.24)

EU legislation concerning veterinary pharmacovigilance:

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. (OJ L311, 28.11.2001, p.1)

Council Regulation (EEC) 2309/93, of 22 July 1993, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. (OJ L214,24.08.1993, p.1)

Commission Regulation (EC) 540/95, of 10 March 1995, laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in the third country, to a medicinal products for human or veterinary use authorised in accordance with the provisions of Council Regulation (EEC) No 2309/93. (OJ L55, 11.03.1995, p.5)

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Commission Regulation (EC) No 1085/2003 of 3 June 2003, concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93. (OJ L159, 27.06.2003, p.24)

Directive 90/220/EEC, of 23 April 1991, on the deliberate release into the environment of genetically modified organisms.(OJ L117, 08.05.1990,p.15)

Member States Council Directive 90/167/EEC, of 26 March 1990, laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community.(OJ L92, 07.04.1990, p.42)

Member States

2. Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

1. Periodic Safety Update Reports for Marketed Drugs

Introduction

1.1 Objectives of the guideline

The main objective of ICH is to harmonise technical requirements for marketing authorisation. However, because new products are introduced at different times in different markets and the same product may be marketed in one or more countries and still be under development in others, reporting and use of clinical safety information should be regarded as part of a continuum.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions (EU, Japan, USA). In order to avoid duplication of effort and to ensure that important data is submitted with consistency to regulatory authorities, this guidance on the format and content for comprehensive periodic safety updates of marketed medicinal products has been developed²¹.

1.2 Background

When a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialisation. Surveillance of marketed drugs is a shared responsibility of the Regulatory Authorities and Marketing Authorisation Holders (MAH). They record information on drug safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, Periodic Safety Update Reports (PSUR) present the world-wide safety experience of a medicinal product at defined times post-authorisation, in order to:

- report all the relevant new safety information from appropriate sources;
- relate these data to patient exposure;
- summarise the market authorisation status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety reevaluation;

²¹ Guidelines are not legally binding. Some portions of this guideline may not be reflected in existing regulations. To that extent, until the regulations are amended, MAHs must comply with existing regulations.

- indicate whether changes should be made to product information in order to optimise the use of the product.

However, if the PSURs required in the different countries where the product is on the market require a different format, content, period covered and filing date, MAH would be required to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonise the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed drugs is different among the three ICH regions. For example:

- The U.S regulations require quarterly reports during the first 3 years, then annual reports. The FDA has recently published proposed rules²² which take into account the CIOMS Working Group II proposals²³.
- In the EU, Council Directive 2001/83/EC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration.
- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorisation. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions which are non-serious, but both mild in severity and unlabeled must be reported every 6 months for 3 years and annually thereafter.

Following a discussion of the objectives and general principles for preparing and submitting PSURs, a model for their format and content is presented. Appended is a glossary of important relevant terms.

1.3 Scope of the guideline

This guidance on the format and content of periodic safety update reports (PSURs) is considered particularly suitable for comprehensive reports covering short periods (e.g. six months, one year) often prepared during the initial years following authorisation.

This guidance might also be applicable for longer term reporting intervals; however, other options may be appropriate.

1.4 General Principles

1.4.1 One report for one active substance

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications or populations (e.g. children vs adults) may be appropriate.

²² Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products; Proposed Rule, Federal Register, 27 October 1994, pp. 54046-54064

²³ International Reporting of Periodic Drug-Safety Update Summaries. Final Report of CIOMS Working Group II, CIOMS - Geneva 1992

For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered important.

1.4.2 General scope of information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorisation applications and renewals, as well as data on serious, unlisted ADRs (see below 1.4.5), which should be cumulative.

The main focus of the report should be adverse drug reactions (ADRs). For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be adverse drug reactions; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions, may represent a significant hazard, and in that sense be a “safety issue”. Although these types of cases should not be included with the usual ADR presentations (i.e. line-listings and summary tabulations), such findings should be discussed within the PSUR (see section 2.8), if deemed medically relevant.

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change (e.g. population exposed, duration of exposure).

1.4.3 Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g. licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data will be duly reported to appropriate regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company’s product information, such data should be included and discussed in the PSUR, even if it is known that it is included in another company’s PSUR.

1.4.4 International birthdate and frequency of review and reporting

Each medicinal product should have as an International Birth Date (IBD), the date of the first marketing authorisation for the product granted to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. When a report contains information on different dosage forms, formulations, or uses (indications, routes, populations), the date of the first marketing authorisation for any of the various authorisations should be regarded as the IBD and, therefore, determine the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cutoff for data to be included in a PSUR.

The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process. In addition, during the initial years of marketing, a drug will ordinarily receive authorisations at different times in

different countries; it is during this early period that harmonisation of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept six-monthly PSURs or PSURs based on multiples of six months. Therefore, preparation of PSURs for all regulatory authorities should be based on data sets of six months or multiples thereof.

Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities.

In addition, approvals beyond the initial approval for the active substance may be granted for new indications, dosage forms, populations, or prescription status (e.g. children vs adults; prescription to non-prescription status). The potential consequences for the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAH since they may influence the requirements for periodic reporting.

The MAH should submit a PSUR within 60 days of the data lock point.

1.4.5 Reference safety information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet"(CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as "Company Core Safety Information" (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an adverse drug reaction is already **LISTED** or is still **UNLISTED**, terms which are introduced to distinguish them from the usual terminology of "expectedness" or "labeledness" which is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited post-marketing safety reporting.

1.4.6 Presentation of data on individual case histories

1.4.6.1 Sources of information

Generally, data from the four following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

- a) Direct reports to MAH (or under MAH control):
 - Spontaneous notifications from health care professionals
 - Spontaneous notifications from non-health care professionals or from consumers (non-medically substantiated)

- MAH-sponsored clinical studies²⁴ or named-patient (“compassionate”) use
- b) Literature
- c) ADR reporting systems of regulatory authorities
- d) Other sources of data:
- reports on ADRs exchanged between contractual partners (e.g. licensors-licensees)
 - data in special registries, such as maintained in organ toxicity monitoring centres
 - reports created by poison control centres
 - epidemiologic databases

1.4.6.2 Description of the reaction

Until an internationally agreed ICH coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology (“controlled vocabulary” or “coding dictionary”) is used by the reporting company.

Whenever possible, the notifying reporter’s event terms should be used to describe the ADR. However, when the notifying reporter’s terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation as possible of the original terms. Under such circumstances, the following should be borne in mind:

- in order to make it available on request, the “verbatim” information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable)
- in the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data
- if a MAH disagrees with a diagnosis that is provided by the notifying health care professional, it may indicate such disagreement within the line listing of cases (see below)
- MAH should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the MAH’s medical interpretation (identified by asterisk or other means).

²⁴ What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between spontaneous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

1.4.6.3 Line listings and/or summary tabulations

Depending on their type or source, available ADR cases should be presented as individual case line listings and/or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting full case reports.

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see 1.4.6.1a) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see 1.4.6.1d) might not be (1) possible without standardisation of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g. all serious ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g. non-serious listed ADRs). Details are set out in section 2.6.4.

2. Model For A Periodic Safety Update Report (PSUR)

The following sections are organised as a sample PSUR. In each of the sections, guidance is provided on what should be included.

SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: (*PRODUCT*)

MAH's NAME AND ADDRESS (*Corporate headquarters or other company entity responsible for report preparation*)

PERIOD COVERED BY THIS REPORT: (*dates*)

INTERNATIONAL BIRTH DATE: Date (*Country of IBD*)

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)

2.1 Introduction

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g. for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (see 1.4.6), the possibility of data duplication should be noted.

2.2 Worldwide Market Authorisation Status

This section of the report provides cumulative information.

Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- dates of market authorisation, and subsequent renewal;
- any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;
- treatment indications and special populations covered by the market authorisation, when relevant;
- lack of approval, including explanation, by regulatory authorities;
- withdrawal by the company of a licence application submission if related to safety or efficacy;
- dates of launch when known;
- trade name(s).

Typically, indications for use, populations treated (e.g. children vs adults) and dosage forms will be the same in many or even most countries where the product is authorised. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures. If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorisations. For multiple authorisations in the same country (e.g. new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorisation date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organised. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

2.3 Update of Regulatory Authority or MAH Actions Taken for Safety Reasons

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission:

- marketing authorisation withdrawal or suspension;
- failure to obtain a marketing authorisation renewal;
- restrictions on distribution;
- clinical trial suspension;
- dosage modification;
- changes in target population or indications;
- formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health profession (e.g. Dear Doctor letters) as a result of such action should also be described with copies appended.

2.4 Changes to Reference Safety Information

The version of the company core data sheet (CCDS) with its company core safety information (CCSI) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PSUR and include the date of last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists and consumers. Therefore, during that period the amended reference document (CCDS) may contain more “listed” information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the official data sheets/product information documents approved in a country, a brief comment should be prepared by the company, describing the local differences and their consequences for the overall safety evaluation and for the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

2.5 Patient Exposure

Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data. While it is recognised that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in

arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric vs adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g. indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

2.6 Presentation of Individual Case Histories

2.6.1 General considerations

- Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.
- With regard to the literature, MAHs should monitor standard, recognised medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once. Also, no matter what “primary source” is given a case, if there is a publication, it should be noted and the literature citation given.

In some countries, there is no requirement to submit medically unconfirmed spontaneous reports that originate with consumers or other non-health care professionals. However, such reports are acceptable or requested in other countries. Therefore, medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

2.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (Table 2); attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources.

- all serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
- all serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient (“compassionate”) use;
- all serious reactions, and non-serious unlisted reactions, from the literature;
- all serious reactions from regulatory authorities

Collection and reporting of non-serious, **listed** ADRs may not be required in all ICH countries. Therefore, a line listing of spontaneously reported non-serious listed reactions that have been collected should be submitted as an addendum to the PSUR only when requested by a regulatory authority.

2.6.3 Presentation of the line listing

The line listing(s) should include each patient only once regardless of how many adverse event/reaction terms are reported for the case. If there is more than one event/reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis),

as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions (e.g. weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organised (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number
- Country in which case occurred
- Source (e.g. clinical trial, literature, spontaneous, regulatory authority)
- Age and sex
- Daily dose of suspected drug (and, when relevant, dosage form or route)
- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).
- Dates of treatment. If not available, best estimate of treatment duration.
- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary). See Section 1.4.6 for guidance.
- Patient outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a “serious” ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

2.6.4 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g. by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the non-serious, **listed**, spontaneously reported reactions (see also 2.6.2).

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see Section 1.4.6).

Except for cases obtained from regulatory authorities, the data on serious reactions from Other Sources (see 1.4.6 c) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e. all cases reported to date) should be provided in the table(s) or as a narrative.

2.6.5 MAH's Analysis of Individual Case Histories

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (Section 2.9).

2.7 Studies

All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

2.7.1. Newly analysed company-sponsored studies

All relevant studies containing important safety information and newly analysed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2.7.2. Targeted new safety studies planned, initiated or continuing during the reporting period

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g. objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analysed, the final results should be presented in a subsequent PSUR as described under 2.7.1.

2.7.3. Published safety studies

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarised and publication reference(s) given.

2.8 Other Information

2.8.1. Efficacy-Related Information

For a product used to treat serious or life threatening diseases, an unusual level of lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2.8.2. Late-Breaking Information

Any important, new information received after the database was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (Section 2.9).

2.9 Overall Safety Evaluation

A concise analysis of the data presented, taking into account any late-breaking information (Section 2.8.2), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:

- A change in characteristics of listed reactions, e.g. severity, outcome, target population
- Serious **unlisted** reactions, placing into perspective the cumulative reports
- Non-Serious **unlisted** reactions
- An increased reporting frequency of **listed** reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.

The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):

- drug interactions
- experience with overdose, deliberate or accidental, and its treatment
- drug abuse or misuse
- positive or negative experiences during pregnancy or lactation
- experience in special patient groups (e.g. children, elderly, organ impaired)
- effects of long-term treatment.

2.10 Conclusion

The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);
- specify and justify any action recommended or initiated.

2.11 Company Core Data Sheet

The Company Core Data Sheet in effect at the beginning of the period covered should be appended to the PSUR.

3 Glossary of Special Terms

Company Core Data Sheet (CCDS) - A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI) - All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which **listed** and **unlisted** are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (Data Cut-off Date) - The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.

International Birth Date (IBD) - The date of the first marketing authorisation for a new medicinal product granted to any company in any country in the world.

Listed Adverse Drug Reaction - An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

Spontaneous Report or **Spontaneous Notification** - An unsolicited communication to a company, regulatory authority or other organisation that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organised data collection scheme.

Unlisted Adverse Drug Reaction - An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the CCSI.

TABLE 1: EXAMPLE OF PRESENTATION OF WORLDWIDE MARKET AUTHORISATION STATUS

Country	Action-Date	Launch Date	Trade Name(s)	Comments
Sweden	A - 7/90	12/90	Bacteroff	-
	AR - 10/95	-	-	-
Brazil	A - 10/91	2/92	Bactoff	-
	A - 1/93	3/93	Bactoff-IV	IV dosage form
United Kingdom	AQ - 3/92	6/92	Bacgone	Elderly (> 65) excluded
	A - 4/94	7/94	Bacgone-C (skin infs)	(PK) Topical cream
Japan	LA - 12/92	-	-	To be refiled
France	V - 9/92	-	-	Unrelated to safety
Nigeria	A - 5/93	7/93	Bactoff	-
	A - 9/93	1/94	Bactoff	New indication
Etc...				

Abbreviations for Action: A = authorised; AQ = authorised with qualifications; LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = Authorisation renewal.

TABLE 2: PRESENTATION OF INDIVIDUAL CASE HISTORIES

(SEE 2.6.2 AND 2.6.4 FOR FULL EXPLANATION)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH <ul style="list-style-type: none"> • Spontaneous ADR reports* • MAH sponsored studies 	S	-	+
	NS U	-	+
	NS L**	+	-
	SA	-	+
2. Literature	S	-	+
	NS U	-	+
3. Other sources <ul style="list-style-type: none"> • Regulatory authorities • Contractual partners • Registries 	S	-	+
	S	+	-
	S	+	-

*** *Medically unconfirmed reports should be provided as a PSUR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.*

** *Line listing should be provided as PSUR addendum only on request by regulatory authorities.
S = serious; L = Listed; A = attributable to drug (by investigator or sponsor); NS = non-serious; U = Unlisted.*

TABLE 3: (EXAMPLE OF SUMMARY TABULATION) #

Number of Reports by Term (Signs, Symptoms and Diagnoses) from Spontaneous (Medically Confirmed), Clinical Study and Literature Cases: All Serious Reactions

(An * indicates an unlisted term)

Body system/ ADR term	Spontaneous/ Regulatory bodies	Clinical studies	Literature
CNS	2	0	0
Hallucinations*	_____	_____	_____
etc.			
etc.			

Sub-total			
CV			
etc.	_____	_____	_____
etc.			

Sub-total			
Etc...			
TOTAL			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms might be given (e.g. x-spontaneous/regulatory y-clinical study, and z-literature cases)

This table is only one example of different possible data presentations which are at the discretion of the MAH (e.g. serious and non-serious in the same table or as separate tables, etc.)

3. Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

Preamble (revision of November 2000)

This revision provides additional information and clarification as well as some modifications of the E2B step 4 document signed off on July 17, 1997. It incorporates adjustments based on the successful pilot projects being conducted in the three regions. It is recommended that the reader reviews this document as well as the M2 ICSR Message Specification document version 2.3. A new attachment 3 provides examples of the use of ICSR identifiers.

1. Introduction

1.1 Scope of this guideline

The objectives of the working group are to standardize the data elements for transmission of individual case safety reports by identifying, and where necessary or advisable, by defining the data elements for the transmission of all types of individual case safety reports, regardless of source and destination. This includes case safety reports for both pre and post approval periods and covers both adverse drug reaction and adverse event reports. It is not intended that this format should be used for cases in the integrated safety summary of a marketing license application dossier. For adverse reactions encountered in clinical trials, this format should be used only for those subject to expedited reporting. The scope of this topic does not encompass the definition of database structures, the design of a paper report form, quality control/quality assurance aspects, or technical security issues.

1.2 Background

Because of national and international laws, rules, and regulations, individual case safety reports of adverse drug reactions and adverse events need to be transmitted, e.g., US 21CFR314.80):

- from identified reporting sources to regulatory authorities and pharmaceutical companies;
- between regulatory authorities;
- between pharmaceutical companies and regulatory authorities;
- within authorities or pharmaceutical companies;
- from clinical investigators, via the sponsor, to ethics committees;
- from authorities to the World Health Organisation (WHO) Collaborating Center for International Drug Monitoring.

The transmission of such individual case safety reports currently relies on paper-based formats (e.g. yellow cards, CIOMS forms, MedWatch...) or electronic media (e.g. within pharmaceutical companies, or with WHO), usually by on-line access, tape or file transfer.

Considering the large number of potential participants in a world-wide exchange of information, there is a need for an electronic format capable of accommodating direct database to database transmission using message transfers.

Successful electronic transmission of information relies on the definition of common data elements, provided in this document, and standard transmission procedures to be specified by the ICH

Electronic Standards for the Transfer of Regulatory Information (ESTRI) Expert Working Group (M2).

This document has taken into account the documents provided by ICH sponsors, the ENS-CARE Single Case Format, EuroSCaPE format, and the CIOMS IA proposal, and comments received following the circulation of these papers.

1.3 Notes on format of this document

Section 2 and its subsections designated A and B contain notes that are directed toward clarifying the nature of the data that should be provided. In addition, there are notes to assist in defining the format that should be used to transmit the data. In order to distinguish between these notes, the user guidances are presented in standard type of a slightly smaller font.

If a data element has a limited set of choices, they are presented in ***bold italic type***. The standard allows for this information to be transmitted in encoded format.

1.4 Definition of Data Elements

The format for individual case safety reports includes provisions for transmitting all the relevant data elements useful to assess an individual adverse drug reaction or adverse event report. The data elements are sufficiently comprehensive to cover complex reports from most sources, different data sets, and transmission situations or requirements; therefore, not every data element will be available for every transmission. In many, if not most instances, a substantial number of the data elements will not be known and therefore not included in the transmission. Where it was deemed important, provisions for unknown/not applicable were included (e.g., outcome, route of administration). However, since the transmission is intended to be electronic, it was thought to be unnecessary to include provisions to assign values of unknown for all data elements. Different ways of including the same data have been provided to cope with differing information contents: e.g., age information can be sent as date of birth and date of reaction/event, age at the time of reaction/event, or patient age group according to the available information (see section B.1.2 and the respective user guidance). In this example, age should be provided by the most precise available data element rather than including multiple elements of redundant data.

Structured data are strongly recommended in electronic transmission and provisions for including information in this way have been made. However, structuring of the data also implies the use of controlled vocabularies, which are not yet available for some data elements. Electronic transmission of individual case safety reports should be implemented with MedDRA where applicable. When MedDRA terms are used the version number should be provided. MedDRA terms should be provided as either text or code according to the regional preferences, until January 2003 when codes will be used in all regions. In certain instances, there are provisions for the transmission of some free text items, including a full text case summary narrative. The transmission of other unstructured data, such as full clinical records or images is outside the scope of this guideline.

A.1.1.5 Minimum information

The minimum information for the transmission of a report should include at least one identifiable patient (section B.1), one identifiable reporter (section A.2), one reaction/event (section B.2), and one suspect drug (section B.4). Because it is often difficult to obtain all the information, any one of several data elements is considered sufficient to define an identifiable patient (e.g., initials, age, sex) or an identifiable reporter (e.g., initials, address, qualification). It is also recognized that the patient and the reporter can be the same individual and still fulfill the minimum reporting criteria.

In addition, to properly process the report, the following administrative information should be provided: the sender's (case) safety report unique identifier (A.1.0.1), the date of receipt of the most recent information (A.1.7), the worldwide unique case identification number (A.1.10) and the sender identifier (A.3.1.2).

2. Guideline: Content of the Data Elements

The message content contains header information followed by E2B Data Elements. See the M2 ICSR Message Specification for information about the header.

The data elements are divided into sections pertaining to:

A: Administrative and Identification Information

A.1 - Identification of the case safety report

A.2 - Primary source(s) of information

A.3 - Information on sender and receiver of case safety report

B: Information on the Case:

B.1 - Patient characteristics

B.2 - Reaction(s)/event(s)

B.3 - Results of tests and procedures relevant to the investigation of the patient

B.4 - Drug(s) information

B.5 - Narrative case summary and further information

A. ADMINISTRATIVE AND IDENTIFICATION INFORMATION

A.1 Identification of the case safety report

A.1.0.1 Sender's (case) safety report unique identifier

User Guidance:

This identifier should remain constant in subsequent transmissions of the case by the same sender. Retransmitters should replace this value with their own unique identifier. The value should be a concatenation of "country code-company or regulator name-report number". Country code is the country of the primary source of the report (A.1.1). The company or regulator name is an internationally unique abbreviation or code for the sender's organisation. The report number is the organisation's international case number. Each component is separated from the other by a hyphen. For example a report transmitted by a company to a regulatory authority concerning a case from France would populate A.1.0.1 with "FR-companyname-12345" where 12345 is a company's unique case report number.

A.1.1 Identification of the country of the primary source

User Guidance:

Generally, this item would be the only country provided. Provisions have been made to include other countries for unusual cases concerning foreign travel and sources of manufactured material (A.1.2 and B.4.k.2.3). See the companion document for appropriate country codes.

A.1.2 Identification of the country where the reaction/event occurred

User Guidance:

For example, this should be the country where the reaction was detected while the patient was traveling, but the report was made by a health professional on the patient's return.

A.1.3 Date of this transmission

User Guidance:

A full precision date should be used (i.e., day, month, year)

A.1.4 Type of report

- Spontaneous report
- Report from study
- Other
- Not available to sender (unknown)

User Guidance:

A separate category for the designation of a literature source is covered in item A.2.2 and is not duplicated in this section which is intended to capture the type of report. If the case in the literature arises from spontaneous observations, "type of report" should be *Spontaneous report*. If the case arises from a study, "type of report" should be *Report from study*. If it is unclear from the literature report whether or not the case(s) cited are spontaneous observations or arise from a study, then this item should be *Other*.

Differentiation between types of studies (e.g. clinical trials or others should be given in section A.2.3.3).

The *Not available to sender* option allows for the transmission of information by a secondary sender (e.g., regulatory authority) where the initial sender did not specify the type of report; it differs from *Other* which indicates the sender knows the type of report but cannot fit it into the categories provided.

A.1.5 Seriousness

A.1.5.1. Serious

-Yes/no

A.1.5.2. Seriousness criteria (more than one can be chosen)

- *Results in death*
- *Is life-threatening*
- *Requires inpatient hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity (as per reporter's opinion)*
- *Is a congenital anomaly/birth defect*

- *Other medically important condition* User Guidance:

The terms *life-threatening* and *other medically important condition* are defined in the ICH E2A guideline. All the criteria apply to the case as a whole and should not be confused with the outcome(s) of individual reactions(s)/event(s)

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that are provided in section B.2.i.8. In addition section B.2.i.3 can be used to identify the seriousness of each reaction/event in accordance with the user guidance of the item.

A.1.6 Date report was first received from source

User Guidance:

For senders dealing with initial information, this should always be the date the information was received from the primary source. When retransmitting information received from another regulatory agency or another company or any other secondary source, A.1.6 is the date the retransmitter first received the information.

A full precision date should be used (i.e., day, month, year).

A.1.7 Date of receipt of the most recent information for this report

User Guidance:

Because reports are sent at different times to multiple receivers, the initial/follow up status is dependent upon the receiver. For this reason an item to capture follow-up status is not included. However, the date of receipt of the most recent information taken together with the "sender identifier" (A.3.1.2) and "sender's (case) report unique identifier" (A.1.0.1) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or follow-up report. For this reason these items are considered critical for each transmission.

A full precision date should be used (i.e., day, month, year).

A.1.8 Additional available documents held by sender

A.1.8.1 Are additional documents available?

- *yes/no*

A.1.8.2 List of documents held by sender

User Guidance:

The documents received from the primary source (e.g., clinical records, hospital records, autopsy reports) should be listed. It is recognized that these documents may not be obtainable in many instances.

A.1.9 Does this case fulfill the local criteria for an expedited report?

- *yes/no*

User Guidance:

The definition of expedited is dependent upon the local regulatory requirements. This item should be used by the sender to indicate if the case fulfills the local expedited requirements. When the countries of origin and destination of the transmission differ, the receiver should be aware that the information might not be applicable to their regulatory requirements.

A.1.10 Worldwide unique case identification number.

User Guidance:

Only A.1.10.1 or A.1.10.2 should be used. No case should ever have more than one of these items completed. The contents of whichever item is used should remain unchanged for any transmissions subsequent to the original transmission. When a regulator is the initial sender A.1.10.1 should be used. When an entity other than a regulator is the initial sender, A.1.10.2 should be used. When a sender has not previously received a valid E2B/M2 report electronically, the identifiers (content and format) in A.1.0.1 and A.1.10.1 or A.1.10.2 should be identical. Retransmitters should use their own sender's (case) safety report unique identifier (A.1.0.1), but not change A.1.10.1 or A.1.10.2. See examples in attachment 3.

A.1.10.1 Regulatory authority's case report number

A.1.10.2 Other sender's case report number

A.1.11 Other case identifiers in previous transmissions

-yes

User Guidance:

This item should be completed only if the answer is yes.

A.1.11.1 Source(s) of the case identifier (e.g., name of the company, name of regulatory agency)

User Guidance:

This repeatable item should be used in conjunction with A.1.11.2 to provide all other case identifiers electronically transmitted, perhaps by multiple other senders. If the case has been received from another sender all other case identifiers included in A.1.11.1 and A.1.11.2 should be present. In addition the identifier of the previous sender (A.1.0.1) should be included here by the retransmitter. See examples in attachment 3.

A.1.11.2 Case identifier(s)

A.1.12 Identification number of the report which is linked to this report (repeat as necessary)

User Guidance:

This section should be used to identify reports or cases that warrant being evaluated together. This includes, but is not limited to, a mother-child pair where both had reactions/events, siblings with common exposure, several reports involving the same patient (e.g., a report sent via paper without a valid E2B/M2 electronic report identifier), several similar reports from same reporter (cluster). This item can also be used when a sender decides to create two or more ICSRs to provide individualised information on two or more suspect drugs in a single case (see B.2.i.7 and B.4.k.13). See examples in attachment 3.

A.1.13 Report nullification

-yes

User Guidance:

This item should be used to indicate that a previously transmitted report should be considered completely void (nullified), for example when the whole case was found to be erroneous. It is essential to use the same case report number previously submitted.

A.1.13.1 Reason for nullification

A.1.14 Was the case medically confirmed, if not initially from a health professional?

-yes/no

User Guidance:

This section should be completed if the primary source of information was a lawyer, consumer, or other non-health professional. It is important because of regional differences in regulations concerning lay reports.

A.2 Primary source(s) of information

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The primary source(s) of the information is a person who reports the facts. This should be distinguished from senders (secondary sources) who are transmitting the information, (e.g., industry to regulatory authority).

Any or all of the three subsections (A.2.1, A.2.2., A.2.3) can be used. In the case of a published study or published individual case, the reporter would be the investigator or first author, and details on publication and trial type should also be provided.

A.2.1 Primary source(s) (repeat as necessary)

A.2.1.1 Reporter identifier (name or initials)

User Guidance:

The identification of the reporter may be prohibited by certain national confidentiality laws or directives. The information should be provided when it is in conformance with the regional confidentiality requirements and this guidance applies to all the subsections of A.2.1. Notwithstanding the above, at least one subsection should be completed to ensure there is an identifiable reporter. If only the name of the reporter is known and providing this name is prohibited because of confidentiality requirements, initials can be used.

A.2.1.2 Reporter's address

User Guidance:

See the companion document for format specifications.

A.2.1.3 Country

User Guidance:

See the companion document for format specifications.

A.2.1.4 Qualification

- *Physician*
- *Pharmacist*
- *Other health professional*
- *Lawyer*
- *Consumer or other non health professional*

User Guidance:

In some regions, consumer and lawyer reports should be transmitted only when there is medical confirmation.

A.2.2 Literature reference(s)

User Guidance:

References are provided in the Vancouver Convention (known as "Vancouver style") as developed by the International Committee of Medical Journal Editors. The standard format as well as those for special situations can be found in the following reference which is in the Vancouver style. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15.

A.2.3 Study identification

A.2.3.1 Study name

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A.2.3.2 Sponsor study number

User Guidance:

This section would be completed only if the sender is the study sponsor or has been informed of the study number by the sponsor.

A.2.3.3 Study type in which the reaction(s)/event(s) were observed

- *Clinical trials*
- *Individual patient use; (e.g. "compassionate use" or named patient basis)*
- *Other studies* (e.g., pharmacoepidemiology, pharmacoeconomics, intensive monitoring, PMS, etc.)

A.3 Information on sender and receiver of case safety report

A.3.1 Sender

A.3.1.1 Type

- **Pharmaceutical company**
- **Regulatory authority**
- **Health professional**
- **Regional pharmacovigilance center**
- **WHO collaborating center for international drug monitoring**
- **Other** (e.g. distributor, study sponsor, or contract research organization)

User Guidance:

In this context, a pharmaceutical company includes biotechnology companies and other manufacturers required to submit individual case safety reports.

A.3.1.2 Sender identifier

User Guidance:

Identifies the sender, (e.g., company name or regulatory authority name). This item should always be completed.

A.3.1.3 Person responsible for sending the report

User Guidance:

Name of person in the company or agency who is responsible for the authorization of report dissemination. This would usually be the same person who signs the covering memo for paper submissions. The inclusion of the name of this person in the transmission may be subject to national or international regulations.

A.3.1.4 Sender's address, fax, telephone and E-mail address

A.3.2 Receiver

User Guidance:

See the user guidance concerning the sender (A.3.1).

A.3.2.1 Type

- *Pharmaceutical company*

- **Regulatory authority**
- **Regional pharmacovigilance center**
- **WHO collaborating center for international drug monitoring**
- **Other** (e.g., a company affiliate or a partner)

A.3.2.2 Receiver identifier (see glossary)

A.3.2.3 Receiver’s address, fax, telephone and E-mail address

B. INFORMATION ON THE CASE

B.1 Patient characteristics

User Guidance:

In cases where a fetus or suckling infant sustains an adverse reaction/event, information on both the parent and the child/fetus should be provided. Reports of these cases are referred to as parent-child/fetus report. Several general principles should be used for filing these reports. If there has been no reaction/event affecting the child/fetus the parent-child/fetus report does not apply. For those cases describing fetal demise or early spontaneous abortion, only a parent report is applicable. If both the parent and the child/fetus sustain adverse events, two reports should be provided but they should be linked by using sections A.1.12 in each of the reports. When only the child/fetus has an adverse reaction/event (other than early spontaneous abortion/fetal demise) the information provided in this section applies to the child/fetus, and characteristics concerning the parent who was the source of exposure to the drug should be provided in section B.1.10.

B.1.1 Patient (name or initials)

User Guidance:

The identification of the patient may be prohibited by certain national confidentiality laws or directives. The information should be provided when it is in conformance with the confidentiality requirements. This also applies to medical record number(s) (B.1.1.1).

B.1.1.1 Patient medical record number(s) and the source(s) of the record number (if allowable)

User Guidance:

Record numbers can include the health professional record(s) number(s), hospital record(s) number(s), or patient/subject identification number in a study. The source of the number should be specified to ensure the possibility of retrieval when possible and desirable.

B.1.2 Age information

User Guidance:

Only one of the elements describing age should be used. The choice should be based upon the most precise information available.

B.1.2.1 Date of birth

User Guidance:

A full precision date should be used (i.e., day, month, year). If the full date of birth is not known an approximate age can be used in section B.1.2.2.

B.1.2.2 Age at time of onset of reaction/event

User Guidance:

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If several reactions/events are in the report, the age at the time of the first reaction/event should be used. For fetal reaction(s)/event(s) the next item B.1.2.2.1 "Gestation period when reaction/event was observed in the fetus" should be used.

When providing the age in decades, please note that, for example, the 7th decade refers to a person in their 60's.

See the companion document for format specifications.

B.1.2.2.1 Gestation period when reaction/event was observed in the fetus

User Guidance:

The gestation period at the time of exposure is captured in section B.4.k.10.

See the companion document for format specifications.

B.1.2.3 Patient age group (as per reporter)

- *Neonate*
- *Infant*
- *Child*
- *Adolescent*
- *Adult*
- *Elderly*

User Guidance:

The terms are not defined in this document and are intended to be used as they were reported by the primary source. This section should be completed only when the age is not provided more specifically in sections B.1.2.1 or B.1.2.2.

B.1.3 Weight (kg)

User Guidance:

The weight at the time of the event/reaction.

B.1.4 Height (cm)

B.1.5 Sex

User guidance:

See the companion document for format specifications.

B.1.6 Last menstrual period date

User guidance:

Imprecise dates can be included, (i.e., month, and year or year only). See the companion document for format specifications.

B.1.7 Relevant medical history and concurrent conditions (not including reaction/event)

B.1.7.1 Structured information on relevant medical history including onset and resolution date as well as relevant comments. (repeat as necessary)

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Disease / surgical procedure / etc.	Start date	Continuing Y/N/U	End date	Comments

User Guidance:

Medical judgment should be exercised in completing this section. Information pertinent to understanding the case is desired such as diseases, conditions such as pregnancy, surgical procedures, psychological trauma, etc. Each of the items in the table can be repeated as appropriate. If precise dates are not known and a text description aids in understanding the medical history, or if concise additional information is helpful in showing the relevance of the past medical history, this information can be included in the Comments column.

If applicable, MedDRA terms should be used in the main descriptive column for disease/surgical procedure/etc. Imprecise dates can be used for both start and end dates. See the companion document for format specifications for the continuing column.

B.1.7.2 Text for relevant medical history and concurrent conditions (not including reaction/event)

User Guidance:

If structured information is not available in the sender's database this item should be used. Otherwise, it is preferable to send structured data in segment B.1.7.1.

B.1.8 Relevant past drug history (repeat the line as necessary)

Name of drug as reported	Start date	End date	Indication	Reactions

User Guidance:

This segment concerns drugs previously taken, but not those taken concomitantly or drugs which may have potentially been involved in the current reaction(s)/event(s). Information concerning concomitant and other suspect drugs should be included in section B4. The information provided here can also include previous experience with similar drugs. Medical judgment should be exercised in completing this section. When completing the item concerning the name of the drug it is important to use the words provided by the primary source. Trade name, generic name or class of drug can be used. The term "none" should be used when appropriate, (e.g., when there is no previous exposure to the drug or vaccine, or no previous reaction following exposure).

If applicable, MedDRA terms should be used in the Indication and Reaction columns. Imprecise dates can be used for both start and end dates.

B.1.9 In case of death

B.1.9.1 Date of death

User Guidance:

An imprecise date can be used. See the companion document for format specifications.

B.1.9.2 Reported cause(s) of death (repeat as necessary)

User Guidance:

MedDRA if applicable

B.1.9.3 Was autopsy done?

Yes/No/Unknown

B.1.9.4 Autopsy-determined cause(s) of death (repeat as necessary)

User Guidance:

MedDRA if applicable

B.1.10 For a parent-child/fetus report, information concerning the parent

User Guidance:

This section should be used in the case of a parent-child/fetus report where the parent had no reaction/event. See user guidance for section B.1. Guidance regarding confidentiality is provided in B.1.1, and should be considered before providing the parent identification. For the subsections B.1.10.4 through B.1.10.8, the guidances provided for B.1.3 through B.1.5 and B.1.7 through B.1.8 should be reviewed.

B.1.10.1 Parent identification

B.1.10.2 Parent age information

User Guidance:

The date of birth should be used if the precise birthday is known; otherwise the age should be used.

B.1.10.2.1 Date of birth of parent

User Guidance:

A full precision date should be used. See the companion document for format specifications.

B.1.10.2.2 Age of parent

B.1.10.3 Last menstrual period date

User Guidance:

A full precision date should be used. See the companion document for format specifications.

If a precise date is not available, the gestation period at time of exposure in B.4.k.10 should be completed.

B.1.10.4 Weight (kg) of parent

B.1.10.5 Height (cm) of parent

B.1.10.6 Sex of parent

B.1.10.7 Relevant medical history and concurrent conditions of parent (not including reaction/event)

B.1.10.7.1 Structured information (parent)

Disease / surgical procedure/ etc.	Start date	Continuing Y/N/U	End date	Comments

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B.1.10.7.2 Text for relevant medical history and concurrent conditions of parent (not including reaction/event)

B.1.10.8 Relevant past drug history of parent

Name of drug as reported	Start date	End date	Indication	Reactions (if any and known)

B.2 Reaction(s)/event(s)

User Guidance:

The designation of “i” in this section indicates that each item is repeatable and that it carries an appropriate correspondence to the same “i” in all subsections. A separate block (i) should be used for each reaction/event term. For example, if two reactions are observed, the first reaction would be described in items B.2.1.0 through B.2.1.8, and the other reaction would be described in items B.2.2.0 through B.2.2.8. The reaction/event specified in the first iteration should be the one used in assessing the intervals in B.4.k.13.

B.2.i.0 Reaction/event as reported by the primary source

User Guidance:

The original reporter's words and/or short phrases used to describe the reaction/event. (The original reporter's words and/or short phrases used to describe reaction/event can also be included in the narrative B.5.1).

B.2.i.1 Reaction/event in MedDRA terminology (Lowest Level Term)

User Guidance:

Only the MedDRA Lowest Level Term (LLT) most closely corresponding to the reaction/event as reported by the primary source should be provided. In the exceptional circumstance when a MedDRA term cannot be found the sender should use good clinical judgment to complete this item with the best MedDRA approximation (see MedDRA™ TERM SELECTION:POINTS TO CONSIDER). MedDRA terms should be provided as either text or code according to the regional preferences until January 2003 when codes should be used in all regions. For international transmissions, English is the generally accepted language.

B.2.i.2 Reaction/event MedDRA term (Preferred Term)

User Guidance:

The term can be a sign, symptom or diagnosis. This also applies to the other items of structured data such as indication, diseases in past medical history, etc. MedDRA terms are to be provided as either text or code according to the regional preferences until January 2003 when codes should be used in all regions. For international transmissions, English is the generally accepted language.

B.2.i.3 Term highlighted by the reporter

1= Yes, highlighted by the reporter, NOT serious

2= No, not highlighted by the reporter, NOT serious

3= Yes, highlighted by the reporter, SERIOUS

4= No, not highlighted by the reporter, SERIOUS

User Guidance:

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A highlighted term is a reaction/event that the primary source indicated was a major concern or reason for reporting the case. If the information is not explicitly provided by the initial reporter the term should not be considered a highlighted term. The seriousness of the reaction/event should be based on the ICH E2A criteria.

B.2.i.4 Date of start of reaction/event

User Guidance:

See the companion document for format specifications.

B.2.i.5 Date of end of reaction/event

B.2.i.6 Duration of reaction/event

User Guidance:

This section can usually be computed from start/end of reaction/event. Both dates and duration may be useful (e.g., for a reaction/event of short duration such as anaphylaxis or arrhythmia). Imprecise dates can be used. See the companion document for format specifications.

B.2.i.7 Time intervals between suspect drug administration and start of reaction/event

User Guidance:

The major uses of intervals are to cover circumstances where both the dates are known but the interval is very short (e.g., minutes, such as in anaphylaxis), and when only imprecise dates are known but more information concerning the interval is known. Dates if available should always be transmitted in the appropriate fields rather than intervals.

B.2.i.7 captures the interval between each reaction/event and only the first iteration of the drug in B.4.k. If there is more than one suspect drug and it is deemed critical, more than one ICSR can be used to provide all the intervals between each reaction/event and all suspect drugs. In this circumstance it is advisable to indicate the reports are linked in A.1.12. The complexity of the intervals highlights the desirability of providing dates. See the companion document for format specifications.

B.2.i.7.1 Time interval between beginning of suspect drug administration and start of reaction/event

B.2.i.7.2 Time interval between last dose and start of reaction/event

B.2.i.8 Outcome of reaction/event at the time of last observation

- *recovered/resolved*
- *recovering/resolving*
- *not recovered/not resolved*
- *recovered/resolved with sequelae*
- *fatal*
- *unknown*

User Guidance:

In case of irreversible congenital anomalies the choice, *not recovered/not resolved* should be used.

Fatal should be used when death is possibly related to the reaction/event. Considering the difficulty of deciding between "reaction/event caused death" and "reaction/event contributed significantly to death", both

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were grouped in a single category. Where the death is unrelated, according to both the reporter and the sender, to the reaction/event, death should not be selected here, but should be reported only under section B.1.9.

B.3 Results of tests and procedures relevant to the investigation of the patient

User Guidance:

This section should capture the tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate (exclude) a non-drug cause, (e.g., serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be reported. While structured information is preferable, provisions have been made to transmit the information as free text in B.3.2.

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B.3.1 Structured information (repeat as necessary)

Date	Test	Result	Unit	Normal low range	Normal high range	More information available (Y/N)

User Guidance:

Imprecise dates can be used, units and normal ranges should be in free text unless covered by a controlled vocabulary. The column entitled "more information available" accepts only yes or no (see the companion document for the appropriate format). If results and units cannot be split, use B.3.2. More than one test can be included in B.3.2.

B.3.2 Results of tests and procedures relevant to the investigation

B.4 Drug(s) information

User Guidance:

This section covers both suspect drugs and concomitant medications including biologicals. In addition, the section can be used to identify drugs thought to have an interaction. For each drug, the characterization of the drug role (B.4.k.1) is that indicated by the primary reporter, (i.e., the original source of the information). The designation of "k" in this section indicates that each item is repeatable and that it carries an appropriate correspondence to the same "k" in all subsections. A separate block (k) should be used for each drug. The drug specified in the first iteration should be the one used in assessing the intervals in item B.2.i.7. Drugs used to treat the reaction/event should not be included here.

B.4.k.1 Characterization of drug role

Suspect/Concomitant/Interacting

User Guidance:

Characterization of the drug as provided by primary reporter. All spontaneous reports should have at least one suspect drug (see Section 1.5). If the reporter indicates a suspected interaction, "interacting" should be selected. All interacting drugs are considered to be suspect drugs.

B.4.k.2 Drug identification

User Guidance:

Drug substance name and/or proprietary medicinal product name should be provided as it was reported. In case of investigational drugs only a code may be known and provided. If more than one active substance is specified, each should be included as a separate drug in item B.4.k.2.2. and repeating the entire drug block (reiteration of "k") rather than as a repeating item B.4.k.2.2. An exception can be made when a proprietary medicinal product is provided in B.4.k.2.1, in which case the active substances can be specified as a repeating item in B.4.k.2.2.

B.4.k.2.1 Proprietary medicinal product name

User Guidance:

The name should be that used by the reporter. It is recognized that a single product may have different proprietary names in different countries, even when produced by a single manufacturer.

B.4.k.2.2 Active substance name(s)

User Guidance:

The INN(s) or drug substance name(s) or drug identification code(s) should be provided if no name exists. For combination products, each active ingredient should be specified. This information, as well as that requested for Proprietary medicinal product name (B.4.k.2.1) may not be known for concomitant or interacting drugs when the sender is a pharmaceutical company. In the case of blinded trials, in the exceptional circumstance

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when the blind has not been broken, the word "blinded" should precede the names of the drugs included in the study. Placebo can be included as a drug.

B.4.k.2.3 Identification of the country where the drug was obtained.

User Guidance:

See the companion document for the appropriate codes and format.

B.4.k.3 Batch/lot number

User Guidance:

This information is particularly important for vaccines and biologicals. The section allows for multiple batch/lot numbers, each separated by a delimiter defined by the transmission standard chosen. The most specific information available should be provided. For expiration date and other related information, see additional information on drug (B.4.k.19).

B.4.k.4 Holder and authorization/application number of drug

User Guidance:

If relevant and known, the name of the holder should be provided with the authorization number in the country where the drug was obtained when the case report is sent to that country. These items apply to both applications and authorizations. Pharmaceutical companies provide this information for their own suspect drug(s).

B.4.k.4.1 Authorization/Application Number

B.4.k.4.2 Country of authorization/application

User Guidance:

See the companion document for the appropriate codes and format.

B.4.k.4.3 Name of holder/applicant

B.4.k.5 Structured Dosage Information

(e.g., 2 mg three times a day for five days)

<i>B.4.k.5.1 dose (number)</i>	<i>2</i>
<i>B.4.k.5.2 dose (unit)</i>	<i>mg</i>
<i>B.4.k.5.3 number of separate dosages</i>	<i>3</i>
<i>B.4.k.5.4 number of units in the interval</i>	<i>1</i>
<i>B.4.k.5.5 definition of the interval unit</i>	<i>day</i>
<i>B.4.k.5.6 cumulative dose to first reaction (number)</i>	<i>30</i>
<i>B.4.k.5.7 cumulative dose to first reaction (unit)</i>	<i>mg</i>

User Guidance:

Please note the above side-by-side illustration of how the structured dosage is provided. For the more complex example of 5mg (in one dose) every other day for 30 days, subsections B.4.k.5.1 through B.4.k.5.7 would be 5, mg, 1, 2, day, 75, mg, respectively. In the same way, 50 mg daily for 2 days would be 50, mg, 1, 1, day, 100, mg. For prolonged chronic therapy, the sender should consider the need to complete the cumulative dose sections.

The cumulative dose provided is the total dose administered until the first sign, symptom or reaction.

In the case of a parent-child/fetus report, the dosage section applies to the parental dose.

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For dosage regimen that involve more than one dosage form and/or changes in dosage, the information should be provided in section B.4.k.6 as text. Alternatively, the sender can provide more than one iteration (k) for the same drug. Categories for "dose unit" and for "definition of the interval" are described in attachment 1.

B.4.k.6 Dosage text

User Guidance:

This item should be used in cases where provision of structured dosage information is not possible.

B.4.k.7 Pharmaceutical form (Dosage form)

User Guidance:

e.g., tablets, capsules, syrup. Free text until a controlled vocabulary is available.

B.4.k.8 Route of administration

User Guidance:

See suggested vocabulary in the route of administration list in Attachment 2. For a parent-child/fetus report this indicates the route of administration of a drug given to the child/fetus. This is usually an indirect exposure such as transmammary but can include more usual routes of administration for other drugs given to the child. The parent's route of administration should be provided in B.4.k.9.

B.4.k.9 Parent route of administration (in case of a parent child/fetus report)

User Guidance:

This section should be used in a parent-child/fetus report and linked parent reports to indicate the route of administration to the parent.

B.4.k.10 Gestation period at time of exposure

User Guidance:

Use the gestational age at the time of the earliest exposure

Gestation period at time of exposure should be expressed by providing both a number and designation of units of days, weeks, months or trimester. See the companion document for format specifications.

B.4.k.11 Indication for use in the case

User Guidance:

The indication as reported. For multiple indications for the same drug, repeat the entire B.4.k block specifying the same drug for each indication. MedDRA terms should be provided as either text or code according to regional preferences until January 2003 when codes should be used in all regions. B.4.k.19 can be used to provide indications in other terminologies.

B.4.k.12 Date of start of drug

B.4.k.13 Time intervals between drug administration and start of reaction/event

User Guidance:

The major uses of intervals are to cover circumstances where both the dates are known but the interval is very short (e.g., minutes, such as in anaphylaxis), and when only imprecise dates are known but more information concerning the interval is known. Dates if available should always be transmitted in the appropriate items, rather than intervals.

B.4.k.13 captures the interval between each drug and only the reaction/event in the first iteration of B.2.i. If there is more than one reaction/event and it is deemed necessary, more than one ICSR can be used to provide all

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the intervals between each suspect drug and all reactions/events. In this circumstance it is advisable to indicate the reports are linked in A.1.12. The complexity of the intervals highlights the desirability of providing dates. See the companion document for format specifications.

B.4.k.13.1 Time interval between beginning of drug administration and start of reaction/event

B.4.k.13.2 Time interval between last dose of drug and start of reaction/event

B.4.k.14 Date of last administration

User Guidance

For ongoing drug administration after the onset of the reaction/event, this item should be blank and Action(s) taken with drug (B.4.k.16) should be used.

B.4.k.15 Duration of drug administration

User Guidance:

This item should be used if exact dates of drug administration are not available at the time of the report, but there is information concerning the duration of drug administration. The information requested is the overall duration of drug administration and covers intermittent administration. See the companion document for the appropriate format.

B.4.k.16 Action(s) taken with drug

- *Drug withdrawn*
- *Dose reduced*
- *Dose increased*
- *Dose not changed*
- *Unknown*
- *Not applicable*

User Guidance:

These data, taken together with the outcome of the reaction (B.2.i.8), provide the information concerning dechallenge. "Not applicable" should be used in circumstances such as if the patient died or the treatment had been completed prior to reaction/event.

B.4.k.17 Effect of rechallenge (or re-exposure), for suspect drug(s) only

B.4.k.17.1 Did reaction recur on readministration?

-yes/no/unknown

User Guidance:

Unknown indicates that a rechallenge was done but it is not known if the event recurred. This segment should not be completed if it is unknown whether a rechallenge was done.

B.4.k.17.2 If yes to item B.4.k.17.1, which reaction(s)/event(s) recurred?

User Guidance:

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Use MedDRA terms

B.4.k.18 Relatedness of drug to reaction(s)/event(s) (repeat B.4.k.18.1 through B.4.k.18.4 as necessary)

User Guidance:

This section provides the means to transmit the degree of suspected relatedness of each drug to the reaction(s)/event(s). The repeating items could also be used to provide the assessment of relatedness by different sources or methods of assessment. For the purpose of reporting, there is an implied suspicion of causality for spontaneous reports. It is recognized that information concerning the relatedness, especially for spontaneous reports, is often subjective and may not be available.

- The following example illustrates the extensive functionality contained in this section.
- Assume a patient being treated with two medications: Drug A and Drug B.
- Assume the patient has had three adverse events: Event 1, Event 2, and Event 3
- The reporter provided assessment of causality for events 1 and 2 for both Drug A and Drug B, but not for either drug concerning event 3. The reporter's assessment of causality is based on overall impression which the sender codes as "global introspection".
- The sender applies two methods of causality assessment, one with an algorithm (coded algorithm) and the other a bayesian analysis which provides a decimal probability (coded Bardi) but it does so only for the drug it manufactures (in this case Drug A).
- From the above there are 4 sets of data for the reporter (2drugsX2eventsX1method of assessment) and 6 sets for the sender (1drugX3eventsX2methods of assessment) for a total 10 sets of data.
- The appropriate item with the information is B.4.k.18 (and its four subfields 1-4). In this example k is replaced by Drug A and Drug B respectively. Please note the subfields 1-4 are repeatable. Thus:

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B.4.k.18.1	B.4.k.18.2	B.4.k.18.3	B.4.k.18.4
k(1) = DRUG A			
event1	reporter	global introspection	related
event1	company	algorithm	possibly related
event1	company	Bardi	0.76
event2	reporter	global introspection	not related
event2	company	algorithm	possibly related
event2	company	Bardi	0.48
event3	company	algorithm	unlikely related
event3	company	Bardi	0.22
k(2) = DRUG B			
event1	reporter	global introspection	not related
event2	reporter	global introspection	not related

The order of the rows is not important since each one represents a complete set, however the E2B message and M2 specifications state that all assessments for Drug A (k=1) appear before Drug B (k=2).

For subsection B.4.k.18.1 MedDRA terms should be used. Subsections B.4.k.18.2 through B.4.k.18.4 do not require a controlled vocabulary.

B.4.k.18.1 Reaction assessed

User Guidance:

Generally the reactions assessed are ordered from the most important or the most serious to the least important.

B.4.k.18.2 Source of assessment (e.g., initial reporter, investigator, regulatory agency, company).

B.4.k.18.3 Method of assessment (e.g., global introspection, algorithm, Bayesian calculation).

B.4.k.18.4 Result

B.4.k.19 Additional information on drug

User Guidance:

This should be used to specify any additional information pertinent to the case that is not covered by above sections. (e.g., beyond expiration date, batch and lot tested and found to be within specifications). This item can also be used to provide additional information concerning the indication for the drug. Regional requirements may involve the use of a controlled vocabulary to provide the additional information concerning indication.

B.5 Narrative case summary and further information

B.5.1 Case narrative including clinical course, therapeutic measures, outcome and additional relevant information.

User Guidance:

Focused, factual and clear description of the case should be given, including the words or short phrases used by the reporter.

B.5.2 Reporter's comments

User Guidance:

This item should be used to include the reporter's comments on the diagnosis, causality assessment or other issues considered relevant.

B.5.3 Sender's diagnosis/syndrome and/or reclassification of reaction/event

User Guidance:

This section provides the sender with an opportunity to combine signs and symptoms that were reported into a succinct diagnosis and the reasoning would be included in section B.5.4. MedDRA terminology.

B.5.4 Sender's comments

User Guidance:

This section provides information concerning the sender's assessment of the case and can be used to describe disagreement with, and/or alternatives to the diagnoses given by the initial reporter.

3. GLOSSARY

Parent-child/fetus report: Report in which the administration of medicines to a parent results in a suspected reaction/event in a child/fetus.

Receiver: The intended recipient of the transmission.

Reporter: Reporter is the primary source of the information, (i.e., a person who initially reports the facts). This should be distinguished from the sender of the message, though the reporter could also be a sender.

Sender: The person or entity creating the message for transmission. Although the reporter and sender may be the same person, the function of the sender should not be confused with that of the reporter.

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DWDFKPHQW 4

Unit List

Mass		Volume	
kg	kilogram(s)	l	litre(s)
g	gram(s)	ml	millilitre(s)
mg	milligram(s)	µl	microlitre(s)
µg	microgram(s)		
ng	nanogram(s)		
pg	picogram(s)		
mg/kg	milligram(s)/kilogram		
µg/kg	microgram(s)/kilogram		
mg/m ²	milligram(s)/sq. meter		
µg/m ²	microgram(s)/ sq. meter		
Radioactivity		Other	
Bq	becquerel(s)	mol	mole(s)
GBq	gigabecquerel(s)	mmol	millimole(s)
MBq	megabecquerel(s)	µmol	micromole(s)
Kbq	kilobecquerel(s)	iu	international unit(s)
Ci	curie(s)	kiu	iu(1000s)
mCi	millicurie(s)	Miu	iu(1,000,000s)
µCi	microcurie(s)	iu/kg	iu/kilogram
nCi	nanocurie(s)	mEq	milliequivalent(s)
		%	percent
		gtt	drop(s)
		DF	dosage form

User Guidance:

This is the suggested list of units. When using other units, transformation is recommended if possible. Otherwise the free text field should be used.

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Definition of Interval List

MinutesHours

Days

Weeks

Months

Years

Cyclical

As necessary

Total

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DWDFKPHQW5

UrxwhriDgp lq lwwdwlrq Olw

Auricular (otic)

Buccal

Cutaneous

Dental

Endocervical

Endosinusal

Endotracheal

Epidural

Extra-amniotic

Hemodialysis

Intra corpus cavernosum

Intra-amniotic

Intra-arterial

Intra-articular

Intra-uterine

Intracardiac

Intracavernous

Intracerebral

Intracervical

Intracisternal

Intracorneal

Intracoronary

Intradermal

Intradiscal (intraspinal)

Intrahepatic

Intralesional

Intralymphatic

Intramedullar (bone marrow)

Intrameningeal

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Intramuscular

Intraocular

Intrapericardial

Intraperitoneal

Intrapleural

Intratumoral

Intratumor

Intrathecal

Intrathoracic

Intratracheal

Intravenous bolus

Intravenous drip

Intravenous (not otherwise specified)

Intravesical

Iontophoresis

Nasal

Occlusive dressing technique

Ophthalmic

Oral

Oropharyngeal

Other

Parenteral

Periarticular

Perineural

Rectal

Respiratory (inhalation)

Retrobulbar

Subconjunctival

Subcutaneous

Subdermal

Sublingual

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Topical

Transdermal

Transmammary

Transplacental

Unknown

Urethral

Vaginal

DWWD F K P H Q W 6

H { dp schv rikrz wr srsxodwh ilhogv uhchydqwwr lghqwi | lqj fdvhdqg wkhlu uhsruw

The figure provides an example of how one would populate the fields relevant to identifying cases and their reports. Patient XX suffers three separate adverse events (AE1, AE2, AE3) spaced over a time period.

H { dp sch rid vlp schvlqjch uhsruwiurp d frp sdq | wr d uhjxodwru

Hospital X reports AE1 to Company K who then in turn sends ICSR1 to Regulator. Population of relevant fields for this case is illustrated in the first row of the table. Company K populates A.1.0.1 with Company K’s (case) safety report unique identifier “JP-K-001”. Company K populates A.1.10.2 with “JP-K-001” because company K is the initial sender of the report. Because there has not been a previous E2B/M2 electronic report, the identifiers in A.1.0.1 and A.1.10.2 are the same.

H { dp sch ri frp sdq | wr frp sdq | wr frp sdq | wr uhjxodwru wudqvp lvvlrq

Hospital X reports AE1 to Company B who then in turn sends ICSR2 to Company C. Population of relevant fields for this case is illustrated in the second row of the table. Company B populates A.1.0.1 with Company B’s (case) safety report unique identifier “JP-B-001”. Company B populates A.1.10.2 with “JP-B-001” because company B considers itself the initial sender of the report because it is unaware that Company K also sent an ICSR for this case.

Company C sends ICSR3 to Company D. The third row of the table indicates how Company C populates the relevant fields. Company C populates A.1.0.1 with “JP-C-001”. Company C populates A.1.10.2 with “JP-B-001”, leaving the field unchanged from the way Company B populated it. In addition, Company C populates A.1.11.1 (Source of the case identifier) with the name of company B, “B”. A.1.11.2 is populated with Case Identifier in the Previous Transmission by Company B “JP-B-001”.

Company D sends ICSR4 to Regulator. The fourth row of the table indicates how Company D populates the relevant fields. Company D populates A.1.0.1 with “JP-D-001”. Company D retains in fields A.1.10.2, A.1.11.1, and A.1.11.2 the information populated by Company C, and Company D adds to the retained information in repeatable field A.1.11.1 “C” to represent that Company C is another source of the case identifier, and Company D adds in field A.1.11.2 “JP-C-001” to represent Company C’s case identifier from the previous transmission.

H { dp sch rid vlp schvlqjch uhsruwz lwk ircorz xs iurp d frp sdq | wr d uhjxodwru

Hospital X reports AE1 to Company E who then in turn sends ICSR5 to Regulator. Population of relevant fields for this case is illustrated in the fifth row of the table. Company E populates A.1.0.1 with Company E’s (case) safety report unique identifier “JP-E-001”. Company E populates A.1.10.2 with “JP-E-001” because company E is the initial sender of the report. Because to Company E’s knowledge, there has not been a previous E2B/M2 electronic report, the identifiers in A.1.0.1 and A.1.10.2 are the same.

ICSR6 represents Hospital X’s follow-up information about AE1 to Company E. Company E submits follow-up to ICSR5 to the regulator. The relevant fields, A.1.0.1 and A.1.10.2, are populated the same as for ICSR5. ICSR6, a follow-up report, is differentiated from ICSR5 by A.1.7, Date of Receipt of the Most Recent Information for this Report.

H { dp sch ri olqn lqj Wz r Vhsdudwh Dgyhuvh Hyhqw D iihfwlqj wkh Vdp h S dwlhqw

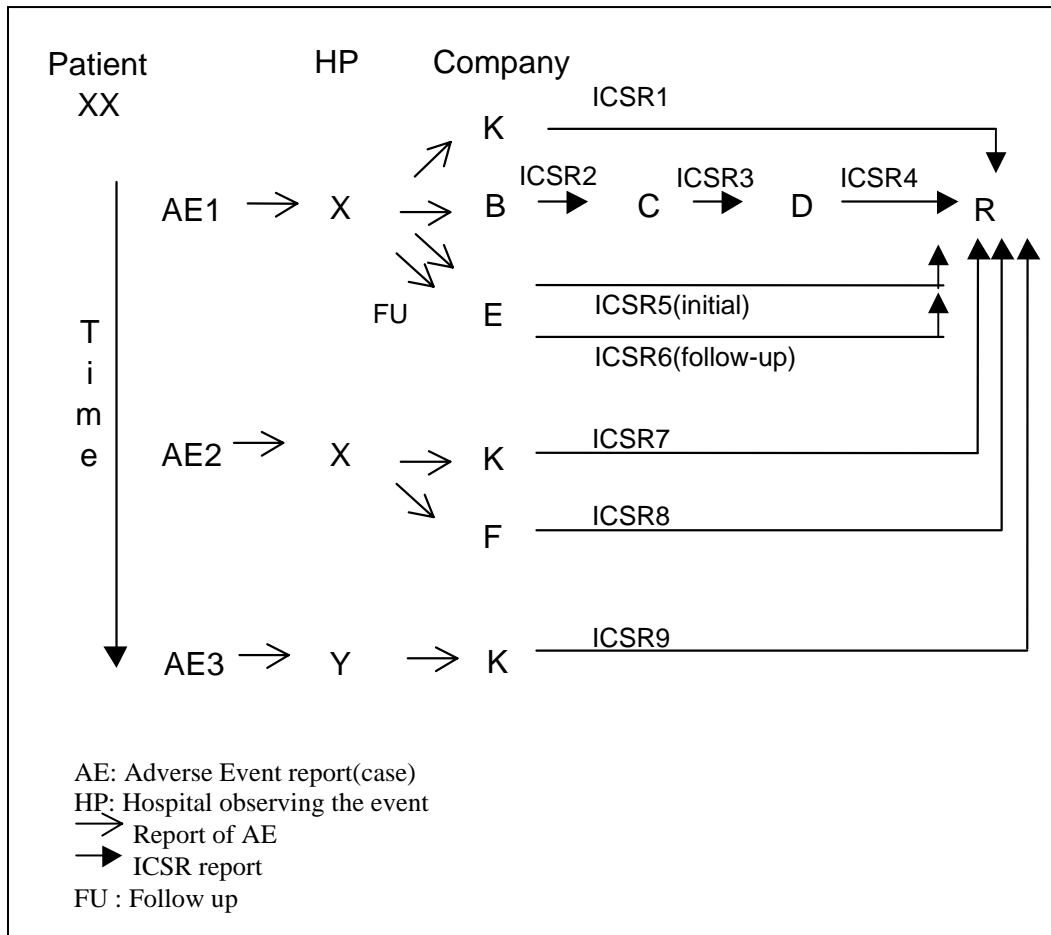
Patient XX later suffers a separate adverse event, AE2. Hospital X reports AE2 to Company K who then in turn sends ICSR7 to Regulator. Population of relevant fields for this new case is illustrated in the seventh row of the table. Company K populates A.1.0.1 with Company K’s (case) safety report unique identifier “JP-K-002”. Company K assigns a new (case) safety report unique identifier “JP-K-002” because “JP-K-001”, as described above, represent a separate adverse event. Company K populates A.1.10.2 with “JP-K-002” because company K is the initial sender of the report. Because there has not been a previous E2B/M2 electronic report, the identifiers

in A.1.0.1 and A.1.10.2 are the same. The previous report from Company K, “JP-K-001”, for patient XX should be represented in A.1.12, Identification Number of the Report which is Linked to this Report.

In a contrasting example, Hospital X also reports AE2 to Company F. Company F had not previously received an AE concerning Patient XX, and therefore there is no linked report and A.1.12 is not populated. As in the first example concerning ICSR1, ICSR8 is a simple single report from a company to a regulator.

H {dp sch riOlqnlqj Wkuhh Vhsdudwh Dgyhuvh Hyhqw D iihfwlqj wkh Vdp h S dwlhqw

Patient XX later suffers a third, separate and distinct adverse event, AE3. Hospital Y reports AE3 to Company K who then in turn sends ICSR9 to Regulator. Population of relevant fields for this new case is illustrated in the ninth row of the table. Company K populates A.1.0.1 with Company K’s (case) safety report unique identifier “JP-K-003”. Company K assigns a new (case) safety report unique identifier “JP-K-003” because “JP-K-001” and “JP-K-002”, as described above, represent separate, adverse events. Company K populates A.1.10.2 with “JP-K-003” because company K is the initial sender of the report. The previous reports from Company K, “JP-K-001” and “JP-K-002”, for patient XX should be represented in the repeatable field A.1.12, Identification Number of the Report which is Linked to this Report.



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Wdexodu uhsuhvhqwdwlrq ri ilhogv frqwhqww iru wkh deryh h{dp schv

A.1.0.1.	A.1.10.2	A.1.11.1	A.1.11.2	A.1.12
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ICSR1(K)	JP-K-001	JP-K-001			
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ICSR2(B)	JP-B-001	JP-B-001			
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ICSR3(C)	JP-C-001	JP-B-001	B	JP-B-001	
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ICSR4(D)	JP-D-001	JP-B-001	B	JP-B-001	
			C	JP-C-001	

ICSR5(E)	JP-E-001	JP-E-001				*
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ICSR6(E)	JP-E-001	JP-E-001				*
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ICSR7(K)	JP-K-002	JP-K-002			JP-K-001
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ICSR8(F)	JP-F-001	JP-F-001			
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ICSR9(K)	JP-K-003	JP-K-003			JP-K-001
					JP-K-002

*These cases have different dates of most recent information (A.1.7)

4. List of Pharmacovigilance documents and guidelines -- Medicinal products for Human Use

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Reference	Document TITLE	Date of Approval by CPMP	Date into operation	Validity? Yes/No Additional Comments
III/3366/91	Procedure for pharmacovigilance exchange of information within the working party	July 91	July 1991	Not valid
III/3445/91	Procedure for causality classification in pharmacovigilance in the European Community	July 1991	July 1991	Not valid
III/3555/91	EC Rapid Alert System : classification of urgency of defective products	January 1993	January 1993	Revised version published 2000*
III/3174/93 III/3176/93 III/3177/93	Guideline on adverse reaction reporting by marketing authorisation holder Guideline for Marketing Authorisation Holders on company-sponsored post-marketing safety studies Guideline for marketing authorisation holders on on-going pharmacovigilance evaluation during the post-marketing period	No	NA	Now incorporated into Part 1, chapter 1 Notice to Marketing Holders – Pharmacovigilance guidelines (NtMH)
III/3175/93	Guideline for marketing authorisation holders on periodic drugs safety update reports			Replaced by Part 1, chapter 1.5
III/3179/93	Report on pharmacovigilance computer systems in EC Member States			Not valid
PhVWP/005/96	Rapid Alert System (RAS) in Pharmacovigilance	May 1996	June 1996 Revised version published 2000	See Part 1, chapter 2.4
E2A ICH/377/95	Nfg on clinical safety data management: Definitions and Standards for expedited reporting	November 1994	June 1995	Yes, published in Volume 3C ²⁵ , valid for clinical trial reporting not for post-marketing,

²⁵ Published in The Rules Governing Medicinal Products in the European Union, Volume 3C, <http://pharmacos.eudra.org/F2/eudralex/Vol-3/home.htm>

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CPMP/PhVWP/175/95	NfG on procedure for competent authorities on the undertaking of pharmacovigilance activities (previously III/3963/92)	June 1995	November 1995 Revised version adopted and published Feb 1999	Yes, see Part 1, chapter 2.1
E2C ICH/288/95	Nfg on clinical safety data management: Periodic Safety updates for marketed drugs	December 1996	June 1997	Yes, published in Volume 3C ²³ and incorporated with slight modifications Part 1, Chapter 1.5, also reproduced for reference purposes, Part IV, chapter 2.
183/97	Conduct of Pharmacovigilance for Centrally Authorised Products	April 1997	April 1997	Yes, see Part 1, chapter 2.2A
PhVWP/99	Conduct of pharmacovigilance for Mutual Recognition procedure			Yes, Part 1,2,3
CPMP/388/97	Crisis Management plan regarding Centrally Authorised products for human use	September 97	September 97	Yes, see Part 1, chapter 2.2B
E2B ICH/287/95	Nfg on clinical safety data management: Data elements for transmission of individual case safety reports	September 1997	March 1998	Yes, see Part IV, chapter 3
PhVWP/053/98	Principles of providing the world health organisation with pharmacovigilance information	January 1998	January 1998	Yes, see Part 1, chapter 2.6
SOP/001/97	Referrals in accordance with the provisions of Council Directive 75/319/EEC in the case of safety concerns related to medicinal products marketed in the European Union	April 1998	April 1998	Yes, see Part 1, chapter 2.5
ICH M2	Recommendations on Electronic transmission of Individual Case Safety Reports message specification	Nov 2000	Nov 2000	Yes ²⁶
CPMP/PhVWP/108/99	Notice to Marketing Authorisation Holders: Pharmacovigilance Guidelines	Jan 99	Jan 99	Yes, see Part I, chapter 1

²⁶ <http://www.emea.eu.int>

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CPMP/PHVWP /1618/01	Position Paper on Compliance with Pharmacovigilance Regulatory obligations	November 2001	January 2002	
CPMP/PhVWP/ 2056/99	Note for guidance on Electronic Exchange of Pharmacovigilance Information for Human and Veterinary Medicinal Products in the European Union	Aug 99	Aug 99	Yes, see Part III
EMEA/H/3138 7/01	Note for guidance Regulatory Electronic Transmission of Individual Case safety Reports (ICSRs) in Pharmacovigilance			Adopted by the Eudravigilance Telematics implementation Group / March 2002
CPMP/ICH/467 9/02	Clinical safety data management periodic safety update reports for marketed drugs.	February 2003		Addendum to ICH E2C

5. List of Abbreviations

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ADR	Adverse Drug Reaction
Agency	European Agency for the Evaluation of Medicinal Products
CVMP	Committee for Veterinary Medicinal Products
CPMP	Committee for Proprietary Medicinal Products
DTD	Data Type Definition
E2B	ICH Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
EDI	Electronic Data Interchange
EU	European Union
EurPh	European Pharmacopoeia
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Reports
IDA	Interchange of Data between Administrations
M2	ICH Specification of the message for the Electronic Transmission of Individual Case Safety Reports
MAH	Market Authorisation Holder
MR	Mutual Recognition
MS	Member State
NUIS	Non-Urgent Information System
PSUR	Periodic Safety Update Report
RAS	Rapid Alert System
SAR	Suspected Adverse Reaction
SGML	Standard Generalised Markup Language
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
VICH	International Co-operation on Harmonisation of Technical Requirements of Veterinary Medicinal Products