DECISION

No. 13/15.06.2007

on approval of Guideline on the procedure to be followed by marketing authorisation holders on undertaking the pharmacovigilance activities

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 15.06.2007, in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Art. 1. – The Guideline on the procedure to be followed by marketing authorisation holders on undertaking the pharmacovigilance activities, according to the Annex which is integral part of this Decision, is approved.

Art. 2. – On the date of the coming into force of this Decision, Scientific Council Decision No. 35/10.12.2004 on approval of Guideline on the procedure to be followed by marketing authorisation holders on undertaking the pharmacovigilance activities, approved through Minister of Public Health Order No. 406/19.04.2005, is repealed.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the procedure to be followed by marketing authorisation holders on undertaking the pharmacovigilance activities

CHAPTER I

General principles

Art. 1. – This Guideline is a translation into Romanian and an adaptation of the chapter „Recommendations for marketing authorisation holders" – Part I – from Eudralex, volume 9a - PHARMACOVIGILANCE.

CHAPTER II

II.1 Legal basis of the marketing authorisation holder's responsibilities concerning the pharmacovigilance activities

Art. 2. – The legal basis of the marketing authorisation holder's (MAH) responsibilities concerning the pharmacovigilance activities for medicinal products for human use Within the European Union (EU) can be found in Regulation No. 726/2004/EC and Law No. 95/2006, on healthcare reform, Title XVII - The medicinal product, which transpose the provisions of the updated Directive No. 2001/83/EC, Chapter X, Pharmacovigilance.

II.2 Roles and responsibilities of MAH and of the qualified person responsible for pharmacovigilance

Art. 3. – (1) The MAH must ensure that it has an appropriate system of pharmacovigilance in place in order to ensure responsibility and liability for its marketed medicinal products and to ensure that appropriate action can be taken, when necessary.

(2) Thus, the DAPP should provide quick and complete reporting to the National Medicines Agency (NMA) and European Medicines Agency (EMEA) of all relevant information concerning the risk-benefit assessment for a medicinal product, in compliance with legislation in force.

Art. 4. – When submitting an application for Marketing Authorisation, the applicant, who prepares to fulfil tasks and responsibilities as a Marketing

Authorisation Holder, should forward a description of the pharmacovigilance system (Law No. 95/2006, Art. 702 (4) k)) as well as the evidence that he/she owns a qualified person responsible for pharmacovigilance, according to Art. 702 (4) q) of Law No. 95/2006, (see Guideline on the requirements for pharmacovigilance systems, compliance monitorisation and pharmacovigilance inspections approved through SCD No. 14/15.06.2007).

Art. 5. –The MAH should have permanently at its disposal a qualified person responsible for pharmacovigilance activities, established in the EU.

Art. 6. – The role of the qualified person responsible for pharmacovigilance is extremely important; this chapter describes his/her role and responsibilities while providing recommendations for the MAH relating to the qualified person responsible for pharmacovigilance.

Art. 7. – Every company (such as the applicant/MAH or MAH group, using a common pharmacovigilance system) ahould appoint one QPPV, responsible for overall pharmacovigilance activity for all medicinal products for which the company holds marketing authorisations within the EU (see SCD No. 14/15.06.2007).

Art. 8. – (1) The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfil the responsibilities and tasks of the post.

(2) If the QPPV is not medically qualified, access to a medically qualified person should be available.

Art. 9. – The name and 24-hour contact details of the QPPV and back-up procedures to ensure business continuity and continued fulfilment of pharmacovigilance obligations should be notified to the NMA, and for centrally authorised products, to the Competent Authorities of all Member States and to the EMEA.

II.2.1 Role and responsibility of the qualified person responsible for pharmacovigilance

Art. 10. – The responsibilities of the qualified person are as follows:

a) the establishment and maintenance/handling of the MAH pharmacovigilance system;

b) having an overview of the safety profiles and any emerging safety concerns (see Glossary in Annex 2 for definition of safety concern) in relation to the medicinal products for which the Marketing Authorisation Holder holds authorisations;

c) acting as a single contact point for the NMA, other Competent Authorities and the EMEA on a 24-hour basis.

Art. 11. – (1) It is recognised that this important role of the QPPV may impose extensive tasks on the QPPV, depending on the size and nature of the pharmacovigilance system and the number and type of medicinal products for which the company holds authorisations.

(2) The QPPV may therefore delegate specific tasks, under supervision, to appropriately qualified and trained individuals, acting as safety experts for certain

medicinal products, provided that the QPPV maintains system oversight and overview of the safety profiles of all medicinal products.

(3) Such delegation should be documented.

Art. 12. – (1) In case of absence, the QPPV should ensure that all responsibilities are undertaken by an adequately qualified person. This person should also reside in the EU (see Footnote 7).

(2) This person should reside in the EU.

Art. 13. – The QPPV should have oversight of the pharmacovigilance system in terms of structure and performance and be in a position to ensure in particular the following system components and processes, either directly or through supervision:

a) 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, and to medical representatives, is collected and collated in order to be accessible at least at one point EU;

b) the preparation for the NMA, where the medicinal product is authorised through centralised procedure, of the reports referred to in Article 816 of Law No. 95/2006, the preparation for the EMEA, the NMA and Competent Authorities of the Member States of the reports referred to in Article 24 of Regulation (EC) No 726/2004; detailed guidance for the preparation of these reports are included in:

- Chapter IV on Individual Case Safety Reports;
- Chapter VI on Periodic Safety Update Reports (PSURs);
- Chapter VII on reports on company-sponsored post-authorisation safety studies.

c) the conduct of continuous overall pharmacovigilance evaluation during the post-authorisation period (see Chapter VIII);

d) the ensuring that any request from the NMA 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; and

e) the provision to the NMA of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation studies and data from sources described in Chapter V.

Art. 14. – The oversight referred to above should cover the functioning of the Marketing Authorisation Holder's pharmacovigilance system in all relevant aspects, including quality control and assurance procedures, standard operating procedures, database operations, contractual arrangements, compliance data (e.g. in relation to the quality, completeness and timeliness for expedited reporting and submission of Periodic Safety Update Reports), audit reports, training of personnel in relation to pharmacovigilance.

Art. 15. – The QPPV should also act as the Marketing Authorisation Holder's contact point for pharmacovigilance inspections or should be made aware by the

Marketing Authorisation Holder of any inspection, in order to be available as necessary.

II.2.2 Responsibilities of the Marketing Authorisation Holder in Relation to the Qualified Person Responsible for Pharmacovigilance

Art. 16. – The MAH should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the fulfilment of the QPPV's responsibilities and tasks.

Art. 17. – (1) The MAH should ensure that there is full documentation covering all procedures and activities of the QPPV and that mechanisms are in place to ensure that the QPPV may receive or seek all relevant information.

(2) The Marketing Authorisation Holder should also implement mechanisms for the QPPV to be kept informed of emerging safety concerns and any other information relating to the evaluation of the risk-benefit balance.

(3) This should include information from ongoing or completed clinical trials and other studies the MAH is aware of and which may be relevant to the safety of the medicinal product, as well as information from sources other than the Marketing Authorisation Holder, e.g. from those with whom the Marketing Authorisation Holder has contractual arrangements.

Art. 18. – The MAH should ensure that the QPPV has sufficient authority in order to:

a) to implement changes to the Marketing Authorisation Holder's pharmacovigilance system in order to promote, maintain and improve compliance; and

b) to provide input into Risk Management Plans (see Chapter III) and into the preparation of regulatory action in response to emerging safety concerns (variations, urgent safety restrictions, and communication to Patients and Healthcare Professionals).

Art. 19. – The MAH should assess risks with potential impact on the pharmacovigilance system and plan for business contingency, including back-up procedures (e.g. in case of non-availability of personnel, adverse reaction database failure, failure of other hardware or software with impact on electronic reporting and data analysis).

II.3 Contractual Arrangements

Art. 20. – (1) A Marketing Authorisation Holder may transfer any or all of the pharmacovigilance tasks and functions, including the role of the QPPV, to another person or organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the Marketing Authorisation Holder.

(2) In such cases, it is the responsibility of the MAH to ensure that detailed and

clear documented contractual arrangements for meeting pharmacovigilance obligations are in place between Marketing Authorisation Holder(s) and persons or organisations involved in the fulfilment of pharmacovigilance obligations and to provide the NMA and, if applicable the EMEA, with information on such arrangements in line with the requirements set out in Guideline on the requirements for pharmacovigilance systems, compliance monitorisation and pharmacovigilance inspections.

(3) The contracted person(s) or organisation should implement quality assurance and quality control systems and accept to be audited by the MAH.

Art. 21. – In cases of contractual arrangements between various MAHs in relation to co-marketing of separately authorised medicinal products which are identical in all aspects apart from their invented names, such arrangements should include measures to avoid the duplicate submission of Individual Case Safety Reports (e.g. literature reports) to EudraVigilance.

CHAPTER III

Requirements for Risk Management Systems

III.1 Introduction

Art. 22. – (1) It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited; this is due to many factors including the small numbers of subjects in clinical trials, restricted population in terms of age, gender and ethnicity, medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

Art. 23. – (1) A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit is judged positive for the target population.

(2) However, not all actual or potential risks will have been identified when an initial authorisation is sought.

(3) In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole.

Art. 24. – (1) Planning of pharmacovigilance activities will be improved if it were more closely based on product-specific issues identified from existing pre - or post-authorisation data and from pharmacological principles.

(2) Such planning will also provide recommendation for electronic data, which are routinely collected within health services to provide rapid investigation of predicted or emerging safety concerns.

Art. 25. – (1) The management of a single risk can be considered as having four steps: risk detection, risk assessment, risk minimisation and risk communication.

(2) However, a typical individual medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity and individual patient and public health impact.

(3) Therefore, the concept of risk management should also consider the combination of information on multiple risks with the aim of ensuring that the benefits exceed the risks by the greatest possible margin both for the individual patient and at the population level.

Art. 26. – (1) This Chapter aims to provide guidance on how the Marketing Authorisation Holder and Applicant should meet the requirements for a description of a risk for an individual medicinal product, or a series of medicinal products, in line with new Community legislation.

(2) This guidance also describes how such a risk management system can be presented to the NMA in the form of a Risk Management Plan (RMP). Art. 27. – Law No. 95/2006 requires Applicants/Marketing Authorisation Holders to provide the NMA with a description of pharmacovigilance and risk management systems.

Art. 28. –The requirements and format for the description of a pharmacovigilance system are covered in the Guideline on the requirements for pharmacovigilance systems, compliance monitorisation and pharmacovigilance inspections, approved as a Scientific Council Decision and should be submitted to the NMA accordingly.

Art. 29. – (1) The present Guideline provides guidance to the Applicant and MAH in the EU on how to meet the requirements for a "detailed description of the risk management system" (see Chapter III, Section 2) and the circumstances when it is appropriate (see Chapter III, Sections 4 and Chapet III Section 14) to provide it.

(2) The risks addressed in this chapter are those related to non-clinical and clinical safety.

(3) Where the disposal of the medicinal product might pose a particular risk because of the remaining active substance (e.g. patches) this issue should also be addressed.

(4) The recommendations in this chapter are applicable to medicinal products in both the pre-authorisation and post-authorisation phase and whether the product was authorised through the centralised, decentralised or mutual recognition procedures.

(5) This Guideline incorporates the concepts of the International Conference on Harmonisation ICH-E2E.

Art. 30. – (1) Article 6 of Regulation (EC) No 726/2004 of Law No. 95/2006 lay down the particulars and documents to be included in an application for the authorisation of a medicinal product for human use.

(2) In accordance with Article 702 (4) k) of Directive No. 95/2006 and in the purposae of this Guideline, the inclusion of a "a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce."is required; this provision forms the legal basis for this chapter.

(3) In the context of centrally authorised medicinal products, Article 9(4) of Regulation (EC) No. 726/2004 requires for a favourable opinion that the following should be attached to the Opinion:

- details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including conditions under which the medicinal product may be made available to the patient, in accordance with the criteria in Chapter VI from Title XVII – The medicinal product of Law 95/2006;

- details of any recommended conditions and restrictions with regards to the safe and effective use of the medicinal product.

Art. 31. – In addition to Article 9(4)(c) of Regulation No. 726/2004/EC, Art.847 of Law No. 95/2006/EC which transposes Article 127 a) of the updated Directive 2001/83/EC states that when a medicinal product is to be authorised in accordance with Regulation (EC) 726/2004 and the Scientific Committee in its opinion refers to recommended conditions or restrictions with regard to the safe and effective use of the medicinal product, a decision addressed to the Member States shall be adopted in accordance with the procedure provided for in Article 741 and 742 of Law No. 95/2006, for the implementation of those conditions or restrictions.

Art. 32. – The legislation provides for additional information to be requested from Marketing Authorisation Holders.

Art. 33. – Article 23 of Regulation (EC) No 726/2004 states that the qualified person shall reside in the Community and shall be responsible for the following:

- ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the risks and benefits of a medicinal product is answered fully and promptly including the provision of information regarding the volume of sales or prescriptions for the medicinal product concerned;

- Providing the NMA with any other information relevant to the evaluation of the risks and benefits of a medicinal product, particularly information concerning post-authorisation safety studies.

Art. 34. – Similarly, for nationally authorised products, Article 815 of Law 95/2006 states that the qualified person shall reside in the Community and shall be responsible for the following:

- ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the risks and benefitsof 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 NMA, 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.

Art. 35. – Article 26 of Regulation (EC) No. 726/2004 states that for a period of five years following the initial placing on the market in the Community, the EMEA may request that the Marketing Authorisation Holder arrange for specific pharmacovigilance data to be collected from targeted groups of patients.

Art. 36. – (1) The detailed description of a risk management system should be provided in the form of an EU Risk Management Plan (EU-RMP) in the situations described in Chapter III.4.

(2) It is strongly recommended that discussions with the NMA on the need for, and content of, an EU-RMP should take place in advance of submission.

III.2. Description of the Risk Management System

Art. 37. – (1) A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

(2) The legislation requires that a description of the risk management system should be submitted when appropriate.

(3) This requirement can be met by the submission of an EU-RMP in the circumstances detailed in Chapter III.4 and III.14.

Art. 38. – (1) The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

(2) This can be done either by increasing the benefits or by reducing the risks but, by its definition, risk management focuses upon the risk reduction approach.

(3) Nevertheless, whenever possible, increases in benefits should also be considered and the characteristics of patients most likely to benefit from treatment should be better defined.

III.3 EU Risk Management Plan (EU-RMP)

Art. 39. – (1) The description of a risk management system should be submitted in the form of an EU-RMP.

(2) The EU-RMP contains two parts:

Part I:

- a safety specification
- a pharmacovigilance plan (PV) and

Part II:

- An evaluation of the need for risk minimisation activities and, if necessary, additional risk minimisation activities (e.g. uncommon, non-routine);
- A risk minimisation plan.

Art. 40. – Part I of the EU-RMP incorporates the concepts of ICH-E2E regarding the Safety Specification, which summarises the safety profile of the medicinal product at the particular point in time of its life-cycle, and the Pharmacovigilance Plan which is based on the Safety Specification.

(2) Chapter III, Sections 6 and 7 of this Guideline include relevant texts from ICH-E2E with additional commentaries on implementation within the EU; section 6.2. also details the particular requirements of the EU for the Safety Specification.

Art. 41. – (1) In Part II of the EU-RMP, on the basis of the Safety Specification, the Applicant/Marketing Authorisation Holder should consider carefully the need for risk minimisation activities to be introduced.

(2) Risk minimisation activities may be "routine" or "additional" (see Chapter III.8).

(3) Within the "evaluation of the need for risk minimisation activities", the Applicant/Marketing Authorisation Holder should provide a full comment on the use of routine risk minimisation activities and whether there is a need for additional risk minimisation activities.

(4) If only routine risk minimisation activities are required there is no need to submit a risk minimisation plan.

(5) If additional risk minimisation activities are thought necessary, the Applicant/MAH should provide a risk minimisation plan within Part II of the EU-RMP.

(6) This risk minimisation plan should contain both the routine and additional activities for each safety concern involved.

(7) Every time the EU-RMP is updated (see Chapter III.14) the Applicant/Marketing Authorisation Holder should reconsider its position vis-à-vis the need for risk minimisation activities and Part II should be updated accordingly.

III.4 Situations requiring an EU-RMP

Art. 42. – (1) The submission of an EU-RMP may be necessary at any time of a medicinal product's life-cycle, during both the pre-authorisation and post-authorisation phases.

(2) In particular an EU-RMP should be submitted:

a) with the application for a new marketing authorisation for:

- any medicinal product containing a new active substance;
- a similar biological medicinal product;
- a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product.

b) in case of a request which implies a significant change in the marketing authorisation (e.g. a new dosage form, a new route of administration, a new manufacturing process of a medicinal product biotechnologically manufactured, significant changes of indications), unless it has been agreed together with the NMA upon not requesting such a submission under those circumstances.

c) on request from the NMA (both pre-authorisation and post-authorisation stages).

d) on the initiative of an Applicant/Marketing Authorisation Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

Art. 43. – In some circumstances, products which are not in the aforementioned categories which are seeking a new authorisation via the centralised procedure may need an EU-RMP:

a) known active substances;

b) hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks;

c) medicinal products with bibliographical documentation ;

d) Fixed combinations.

Art. 44. – For situations where the submission of an EU-RMP is not mandatory, the need for it should be discussed with the NMA.

III.4.1 Marketing authorisation via the centralised procedure

Art. 45. – At any stage, but in particular during the pre-authorisation phase, an Applicant/MAH may request advice on the need for, development or content of an EU-RMP through the scientific advice procedure.

Art. 46. – Whether or not the scientific advice procedure has been used, discussion on the EU-RMP for a medicinal product seeking a new authorisation through the centralised procedure should take place at the pre-submission meeting.

Art. 47. – (1) For significant changes to an existing centralised marketing authorisation, the Marketing Authorisation Holder should discuss the need for an EU-RMP with the EMEA at least two months in advance of the submission.

(2) When it is not mandatory that an EU-RMP is submitted and the Applicant/Marketing Authorisation Holder thinks it is unnecessary, the Applicant/Marketing Authorisation Holder should submit a brief justification of this along with the application which will form part of the formal assessment by the Rapporteur.

(3) However, it is strongly recommended that this is discussed with the EMEA before the submission of the application.

III.4.2 Marketing Authorisation via the Mutual Recognition or Decentralised Procedure

Art. 48. – (1) The Competent Authority of the Member State should be contacted regarding the timings of discussions on Risk Management Plans.

(2) Where there is a Reference Member State (RMS), the Competent Authority of this country should be consulted.

III.5 Location in the Application

Art. 49. – (1) An EU-RMP submitted at the time of an application for a Marketing Authorisation should be provided in Module 1 of the Marketing Authorisation Application in a stand-alone format allowing circulation to, and evaluation by the pharmacovigilance and risk management experts.

(2) The EU-RMP should be accompanied by other relevant documents such as study protocols, where applicable.

Art. 50. – (1) Updates to the EU-RMP (see Chapter III.14) should be presented preferably in a tab-separated dossier and in accordance with the approriate headings and numberings of the EU-CTD format.

(2) This should be accompanied by a cover letter, detailing which sections of the EU-RMP have been changed, as well as study reports (if appropriate).

III.6 Safety Specification

Art. 51. – (1) The Safety Specification should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information.

(2) It should also address the populations potentially at risk (where the medicinal product is likely to be used), and outstanding safety issues which warrant further investigation to refine understanding of the risk-benefit profile during the post-authorisation period.

(3) The Safety Specification is intended to help industry and competent authorities identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan.

Art. 52. – In the EU-RMP the Safety Specification will form the basis of the evaluation of the need for risk minimisation activities and, where appropriate, the risk minimisation plan.

Art. 53. – (1) It is recommended that Applicants/Marketing Authorisation Holders follow the structure of elements provided below when compiling the Safety Specification.

(2) The elements of the Safety Specification that are included are only a guide.

(3) The Safety Specification can include additional elements, depending on the nature of the medicinal product and its development programme.

(4) Conversely, for medicinal products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

III.6.1 Non-clinical Part of the Safety Specification

Art. 54. – Within the Safety Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, such as:

a) Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);

b) General pharmacology (cardiovascular, including QT interval prolongation, nervous system);

c) Drug interactions;

d) Other toxicity-related information or data.

Art. 55. – (1) The relvance of the findings to the use in humans should be discussed.

(2) If the medicinal product is intended for use in special populations, consideration should be given to whether specific non-clinical data exist.

III.6.2 Clinical Part of the Safety Specification
III.6.2.1 Limitations of the Human Safety Database

Art. 56. – (1) Limitations of the safety database (e.g. related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

(2) Particular reference should be made to populations likely to be exposed during the intended or expected use of the medicinal product in medical practice.

Art. 57. – (1) In order to assess the limitation of the human safety database, the size of the study population should be detailed using both numbers of patients and patient-time (patient-years, patient-months) exposed to the medicinal product.

(2) This should be stratified, for relevant population categories such as age and gender, type of study (e.g. randomised controlled trial, open clinical trial, observational study) and any other relevant variable, such as dose, indication and duration of treatment.

(3) Limitations of the database should also be presented in terms of the frequencies of adverse drug reactions detectable given the size of the database.

(4) The limitations of the database should also be discussed with regard to suspected long-term adverse reactions (e.g. malignancies) when it is unlikely that exposure data is of sufficient duration and latency.

Post-marketing (non-study) exposure

Art. 58. – (1) Where marketing of the medicinal product has occurred, the applicant/MAH should provide data on post-marketing exposed patients.

(2) Exposure data based on the numbers of kilogrammes of medicinal product sold divided by the average dose is only valid if the medicinal product is always taken at one dose level for a fixed length of time– which is not the situation with most medicinal products.

(3) In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other measures should be used as well.

Art. 59. – (1) A more accurate method of patient exposure based on market research should be provided where possible.

(2) When deciding which measure to use for exposure data, it is important to consider the way a medicinal product is used.

(3) For example, for medicinal products used chronically, the appropriate measure may be patient-years of use.

(4) However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be appropriate.

(5) The informaion should be stratified by relevant variables such as age, indication, dose and duration of treatment.

III.6.2.2 Populations not studied in the pre-authorisation stage

Art. 60. – (1) The safety specification should discuss which populations have not been studies or have only been studied to a limited degree in the pre-authorisation phase.

(2) The implications, with respect to predicting the safety of the medicinal product in the marketplace should be explicitly discussed.

Art. 61. – (1) Limitations of the database should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population, in particular when exclusion criteria are not proposed as contraindications for the medicinal product.

(2) In discussing differences between target population and the one exposed in clinical trials, it should be taken into account that certain differences may be generated by the trial sites (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria.

Art. 62. –Populations to be considered for discussion should include (but might not be limited to):

a) children;

b) the elderly;

c) pregnant or lactating women;

d) patients with relevant co-morbidity such as hepatic or renal disorders;

e) patients with disease severity different from that studied in clinical trials;

f) sub-populations carrying known and relevant genetic polymorphism;

g) Patients of different racial and/or ethnic origins.

Post-Marketing Experience:

Art. 63. – For updates to the Safety Specification, specific reference should be made to how the realised pattern of exposure (including off-label use) has differed from that predicted and from the indication(s) and contraindications in the Summary of Product Characteristics.

Art. 64. – Newly identified safety concerns should be mentioned; any issue found in relation to a population not studied in the pre-approval phase should particularly be discussed along with the implications for the Summary of Product Characteristics.

Art. 65. – Regulatory actions taken in relation to a safety concern should be mentioned.

III.6.2.3 Adverse Events/Adverse Reactions

Art. 66. –This section should list the important identified and potential risks that require further characterisation or evaluation.

Identified risks that require further evaluation

Art. 67. – (1) More detailed information should be included relating to the most important identified adverse events/adverse reactions, which would include those

that are serious or frequent and that also might have an impact on the balance of benefits and risks of the medicinal product.

(2) Such information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available.

(3) Risk factors and potential mechanisms should be discussed.

(4) These adverse events/adverse reactions should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g. frequency in normal conditions of use, severity, outcome, at-risk groups).

Potential risks that require further evaluation

Art. 68. – (1) Significant potential risks should be presented in this section.

(2) The evidence that lead to the conclusion that there is a potential risk should be presented.

(3) It is anticipated that for any important potential risk, there should be further evaluation to characterise the association.

Presentation of risk data

Art. 69. –When the information is available, detailed risk data should be presented according to the following articles.

Art. 70. – (1) The frequency of important adverse reactions should be expressed taking into account the source of the data.

(2) For a medicinal product already on the market, the reporting rate based on the number of spontaneously reported adverse events/adverse reactions and the sales data is very likely to underestimate the rate of occurrence of an adverse reaction in an exposed population.

(3) When an accurate frequency is needed for an important adverse reaction, this shoull always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number of patients exposed to the medicinal product and the number of patients who experienced the respective adverse event/adverse reaction are known.

Art. 71. – (1) The denominator should be expressed using the appropriate measure: e.g. number of patients or in patient-time or equivalent units (courses of treatment, prescriptions).

(2) It should be stated clearly which frequency parameter is being used: e.g. incidence proportion (patient units in the denominator) or incidence rate (patient-time units in the denominator).

(3) Confidence intervals should be provided.

(4) When using the patient-time unit, the underlying assumption is that the hazard function must be nearly constant over the follow-up time.

(5) Otherwise it should be split into relevant categories where the assumption of constancy holds.

(6) Where appropriate, the period of major risk should be identified.

(7) Adverse event/adverse reaction incidence rates should be presented for the whole population and for relevant population categories.

Art. 72. – (1) For important identified risks, the excess and relevant incidence should be given.

(2) Excess incidence (in comparison to placebo and active comparator, if available) should be calculated based on the best available evidence (e.g. meta-analytic techniques) for each population (total controlled, total controlled plus open label extension, open study).

(3) The period prior to event data should be summarised using the survival technique which takes appropriate account of the „censored" information.

(4) Cumulative hazard functions may provide a simple visual comparison of the competing risks of different adverse reactions.

(5) These data can be stratified by substance (to investigate the difference in the adverse event profile between active and placebo), or by risk factors such as dose, gender or age.

Art. 73. – (1) The potential impact of the most important identified and important potential risks should be addressed using for example: strength of evidence, supporting plausibility, nature of evidence and potential public health burden, morbidity and case fatality.

(2) Recording these in a structured form will facilitate assessment of the potential significance of the safety concern.

(3) Classification of the safety concern by dose, time and risk factors is encouraged.

(4) The identification of susceptible patients should receive specific attention, possibly from analysis of cases.

(5) It is likely that the adverse reactions will require further evaluation as part of the Pharmacovigilance Plan.

III.6.2.4 Identified and Potential interactions including food-drug and drug-drug interactions.

Art. 74. – (1) Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed.

(2) For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed.

Art. 75. – It should be stated which interactions require further investigation.

III.6.2.5 Epidemiology

Art. 76. – (1) The epidemiology of the indication(s) should be discussed.

(2) This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin.

(3) Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in the EU.

Art. 77. – (1) In addition, for important adverse events that may require further investigation, it is useful to review the incidence rate of these events among patients in whom the medicinal product is indicated (i.e. the background incidence rates).

(2) Information on risk factors for an adverse event would also be useful to include, if available.

(3) For example: if a medicinal product is intended for treating prostate cancer the target population is likely to be men over the age of 50 years; this population is also at increased risk of myocardial infarction.

(4) If it is suspected that the medicinal product might also cause myocardial infarction, it would be useful to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not on the medicinal product.

III.6.2.6 Pharmacological class effects

Art. 78. –The Safety Specification should identify risks believed to be common to the pharmacological class.

Art. 79. –If a risk which is common to the pharmacological class is not thought to be a safety concern with the medicinal product, this should be justified.

III.6.2.7 Additional EU Requirements

Art. 80. – (1) The Applicant/MAH is requested to discuss the topics below.

(2) If the potential is thought to be significant, the topic should be identified as an important potential risk and means for reducing or minimising it discussed in the chapter on the "Evaluation of the need for risk minimisation activities".

(3) In this context, "significant" means that there is a reasonable likelihood that it will occur.

(4) Where a particular topic is not relevant to the individual medicinal product, this should be stated along with the reason.

Potential for overdose

Art. 81. –Special attention should be given in particular cases, e.g. where there is a narrow therapeutic margin, a medicinal product with significant toxicity and/or an increased risk of overdose in the target population.

Potential for transmission of infectious agents

Art. 82. –The Applicant/Marketing Authorisation Holder should discuss the potential for the transmission of infectious agents in line with Chapter V.

Potential for misuse for illegal purposes

Art. 83. – (1) The potential for misuse for illegal purposes should be considered.

(2) If appropriate, the means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the RMP Chapter "Evaluation of the Need for Risk Minimisation Activities".

Potential for off-label use

Art. 84. – (1) The potential should be discussed.

(2) This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons.

(3) The potential for use in other disease areas should also be considered where this is likely.

Potential for off-label paediatric use

Art. 85. – If the disease or disorder which is being treated or prevented is found in the paediatric population, the potential for off-label paediatric use in the non-authorised age groups should be discussed.

III.6.3 Summary

Art. 86. – At the end of the Safety Specification a summary should be provided of the:

a) Important identified risks;

b) Important potential risks;

c) Lack of important information.

Art. 87. – Based on this summary the Applicant/Marketing Authorisation Holder should provide a Pharmacovigilance Plan and an evaluation of the need for risk minimisation activities (see Template in Annex 5.1.1).

III.7 Pharmacovigilance plan

Art. 88. – (1) According to ICH-E2E, the Pharmacovigilance Plan should be based on the Safety Specification and propose actions to address the safety concerns identified.

(2) Early discussions between the NMA and the Applicant/Marketing Authorisation Holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed.

(3) It is important to note that only a proportion of risks are likely to be foreseeable and the Pharmacovigilance Plan will not replace but rather complement the procedures currently used to detect safety signals.

III.7.1 Routine Pharmacovigilance

Art. 89. – For medicinal products where no special concerns have arisen, routine pharmacovigilance should be sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies).

Art. 90. –A desciption of routine pharmacovigilance activities is covered elsewhere in Part I of the EU-RMP, which should be consulted in developing the Pharmacovigilance Plan.

III.7.2 Additional Pharmacovigilance Activities and Action Plans

Art. 91. – For medicinal products with important identified risks, important potential risks, or important missing information, additional activities designed to address these safety concerns should be considered.

Art. 92. – (1) Applicants/Marketing Authorisation Holders should also consider the situations when routine pharmacovigilance is likely to be inadequate.

(2) An example of this might be when a potential risk with an individual medicinal product has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the "normal" incidence.

(3) When any doubt exists about the need for additional pharmacovigilance activities, consultation with the NMA should be considered.

Art. 93. – (1) The objective(s) of additional pharmacovigilance activities shall normally be identified according to the safety concern to be addressed.

(2) For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association.

(3) For important missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

Art. 94. – (1) The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health.

(2) For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer.

Art. 95. – (1) The Table VII.A lists some of the epidemiological activities which might be considered necessary for inclusion in a Pharmacovigilance Plan.

(2) Additional pharmacovigilance activities included in the Pharmacovigilance Plan should be designed and conducted according to the recommendations in the Guidelines for Good Pharmacoepidemiology Practices.

(3) For studies involving children, the Guideline on Conduct of Pharmacovigilance for Medicinal Products used by the paediatric population should be consulted.

(4) The responsibility for the scientific value of the study's protocol remains with Applicants/Marketing Authorisation Holders, even if previous discussions have taken place with the NMA.

III.7.3 Action plan for safety concerns

Art. 96. – Within the Pharmacovigilance Plan the action plan for each safety concern should be presented and justified according to the following structure (see also EMEA/20732/2007 document):

a) safety concern;

b) objective of proposed action(s);

c) rationale form proposed action(s);

d) Monitoring by the Applicant/Marketing Authorisation Holder of the safety concern and proposed action(s);

e) Milestones for evaluation and reporting.

Art. 97. – (1) Protocols (draft or otherwise) for any formal studies should be provided.

(2) Details of the monitoring for the safety concern in a clinical trial could include: stopping rules, information on the drug safety monitoring board and when interim analyses will be carried out.

Art. 98. – (1) Although not explicitly included in this structure, it is also necessary in the EU-RMP to explain the decision making processes which will depend on the outcomes of the proposed actions.

(2) The possible consequences of the study outcomes should be discussed.

III.8. Evaluation of the need for risk minimisation activities

Art. 99. – On the basis of the Safety Specification, the Applicant/Marketing Authorisation Holder should provide an evaluation of the need for risk minimisation activities.

Art. 100. – (1) For each safety concern, the Applicant/Marketing Authorisation Holder should assess whether any risk minimisation activities are needed.

(2) Some safety concerns may be adequately addressed by the proposed actions in the Pharmacovigilance Plan but for others the risk may be of a particular nature and seriousness that risk minimisation activities are needed.

(3) It is possible that the risk minimisation activities may be limited to ensuring that suitable warnings are included in the medicinal product information or by the careful use of labelling and packaging, i.e. routine risk minimisation activities.

(4) If an Applicant/Marketing Authorisation Holder considers that no additional risk minimisation activities beyond warranted ones are needed, this should be discussed and, where appropriate, supporting evidence provided.

Art. 101. – (1) However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary.

(2) If these are required, they should be described in the risk minimisation plan (see Chapter III.9) which should be included in Part II of the EU-RMP.

Art. 102. – Within the evaluation of the need for risk minimisation activities, the Applicant/Marketing Authorisation Holder should also address the potential for medication errors (see Chapter III.8.1) and state how this has been reduced in the final design of the pharmaceutical form, medicinal product information, packaging and, where appropriate, device.

Art. 103. – (1) As a rule, Applicants/Marketing Authorisation Holders should always consider the need for risk minimisation activities even if the Safety Specification is updated in the light of new safety information on the medicinal product.

(2) In some circumstances, it may be appropriate to suggest that an additional risk minimisation activity be stopped because experience with the medicinal product suggests that it is no longer necessary for the safe and effective use.

III.8.1. Potential for Medication Errors

Art. 104. – (1) Applicants/Marketing Authorisation Holders are encouraged routinely to consider the likelihood of medication errors.

(2) In particular, they should assess prior to marketing, common sources of medication errors.

(3) During the development phase and during the design of the medicinal product for marketing, the Applicant needs to take into account potential reasons for medication error.

(4) The naming (taking into account the Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed through the Centralised Procedure), presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered.

Art. 105. – (1) If a medicinal product has life-threatening potential when administered by an incorrect route, consideration should be given as to how such administration can be avoided.

(2) This issue is particularly important when it is common practice to administer the medicinal product at the same time as other medicinal products given by the hazardous route.

Art. 106. – (1) The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed.

(2) In case of medicinal products which are likely to be used by a visually impaired population, special consideration should be given to the potential for medication error.

Art. 107. – Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Art. 108. – (1) Medication errors identified during the medicinal product's development should be discussed and information on the errors, their potential cause(s) and possible remedies given.

(2) Where applicable an indication should be given of how these have been taken into account in the final medicinal product design.

Art. 109. – If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated EU-RMP and ways of limiting the errors proposed.

III.9 The risk minimisation plan

Art. 110. – (1) The risk minimisation plan details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern.

(2) When a risk minimisation plan is provided within an EU-RMP, the risk minimisation plan should include both routine and additional risk minimisation activities.

(3) In case of a safety issue, there is a possibility that a single object implies several risk minimisation activities.

(4) For example, a possible plan for a known teratogen effect could have the objective of avoiding any pregnant patient taking the medicinal product.

(5) A routine risk minimisation activity might be to emphasise the need for effective contraception in the Summary SPC and a recommendation that patients should have a negative pregnancy test before each prescription.

(6) One additional risk minimisation activity might be to develop an educational pack to provide information to the patients on the risks of the medicine and the need for contraception.

(7) It might also be an activity to limit the pack sizes to one month's supply of the medicinal product.

Art. 111. – (1) The risk minimisation plan should list the safety concerns for which risk minimisation activities are proposed.

(2) The risk minimisation activities, i.e. both routine and additional, related to that safety concern should be discussed.

(3) For each safety concern the following headings in the plan will mirror those for safety concerns listed in Chapter III.7.3.

(4) In addition, for each proposed additional risk minimisation activity, a section should be included detailing how the effectiveness of it as a measure to reduce risk will be assessed (see document EMEA/20732/2007).

III.10 Risk minimisation activities

Art. 112. – (1) It is difficult to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis.

(2) Some of the risk minimisation activities are described in the Table III.A at the end of this Chapter, but it is essential that appropriate specialised experts are consulted at all stages and Marketing Authorisation Applicants and Holders are also encouraged to discuss risk minimisation plans with the NMA early on.

III.10.1 Risk communication

Art. 113. – (1) Accurate and timely communication of emerging data on risk is an essential part of pharmacovigilance.

(2) Risk communication is an important step in risk management as well as a risk minimisation activity.

(3) Patients and healthcare professionals need accurate and appropriately communicated information about the risks associated with both the medicinal product, and the condition for which it is being used, so that an informed choice can be made about the most appropriate treatment.

(4) The medicinal product information in the form of the Summary of Product Characteristics and Patient Information Leaflets is an important means of informing prescribers and patients about the risks associated with a particular medicine but additional materials may be needed.

(5) A short list of established media for such communication is given in the Table III.A (Chapter "Additional Educational Material"), but the target audience, levels of detail required to achieve effective results and the most appropriate forms of words will vary will all vary with circumstances.

(6) Whereas Marketing Authorisation Holders may produce educational material to inform and educate Healthcare Professionals and Patients, the requirement to do this will only be included as a condition of the marketing authorisation when it is deemed necessary for the safe and effective use of the medicinal product.

Art. 114. –Because of the importance of risk communication it is recommended that appropriate experts are consulted.

III.11 The Marketing Authorisation

Art. 115. – (1) Restrictions and conditions within the marketing authorisation may be used as a risk minimisation activity (see Table III.A.).

(2) When a marketing authorisation is granted, it should include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to the patient.

(3) These conditions may also be modified when the marketing authorisation is amended in the post-authorisation phase.

(4) This issue is commonly referred to as the "legal status" of a medicinal product.

(5) It may also restrict where the medicinal product can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist).

(6) For medicinal products only available upon prescription, additional conditions may be imposed by classifying medicinal products as available only upon either a restricted medical prescription or a special medical prescription.

Art. 116. – (1) The CHMP or National Competent Authorities may also make recommendations on conditions or restrictions with regard to the safe and effective use of the medicinal product.

(2) In the case of the CHMP, these conditions or restrictions will usually only affect the European Commission (EC) Decision addressed to the Marketing Authorisation Applicant.

(3) However, in certain circumstances, the European Commission may also adopt a decision addressed to the Member States.

III.12 Ensuring the Effectiveness of Risk Minimisation Activities

Art. 117. – (1) The definition of risk management requires assessment of the effectiveness of the interventions forming part of the process.

(2) It is clearly desirable that activities which may involve substantial investment of effort and resources should be shown to achieve the desired effects.

(3) In addition, as a public health measure it is imperative that alternative methods be adopted should a particular risk minimization strategies prove ineffective.

(4) Assessment of effectiveness will also increase understanding of which activities are most appropriate in addressing specific types of safety concerns.

III.12.1 Assessment of Risk Minimisation

Art. 118. – (1) A direct measurement of risk minimisation should be employed whenever feasible. Surrogate measures should be considered when this is not feasible or to provide interim assessments whilst awaiting direct risk minimisation measurements.

(2) For example, for measures based on the provision of information to professionals, descriptive studies or surveys which assess whether the information is being effectively communicated might be appropriate.

(3) The use of medical databases might also allow direct measures of how uniformly such advice was being adhered to by reviewing, for example, concomitant medication or the results of laboratory tests.

(4) Since such studies are likely to be required with increasing frequency, the availability of such databases will be an ever more important factor in risk management.

(5) If the prescribing databases are further linked to patient clinical outcome, a study of the adequacy of the prescribing process could be designed to evolve over time into a full risk reduction study.

Art. 119. – (1) It is clear that, even when risks are of a type which can be directly measured, ethical and practical considerations may prevent prospective comparison.

(2) It may be scientifically difficult to make direct comparison between a situation with and without the intervention to be assessed and may not be achievable in time scales which allow the lesson learned to be used to improve risk management.

(3) In particular this will occur when risks associated with long-term exposure or very rare events are to be reduced.

(4) For medicinal products where a risk minimisation plan has been introduced after some time on the market a comparison with historical data can be made.

(5) Not withstanding the above, the applicant/MAH should investigate new methodologies for monitoring and assessment.

III.13 Summary of Activities in the EU-RMP

Art. 120. – (1) The EU-RMP should contain an overall summary of the activities detailed for the medicinal product.

(2) This should be structured in two parts:

a) Summary of activities for each important safety concern;

b) Summary of all activities and their milestones.

Art. 121. –The relationship between activities and safety concerns may be clarified by a cross-tabulation of the two categories showing which safety concerns are addressed by each activity.

Summary of activities for each safety concern:

Art. 122. – (1) This should be a simple table, listing each safety concern and summarising the activities (both pharmacovigilance and, where appropriate, risk minimisation) which will be taken.

(2) Where appropriate, it should provide a cross-reference to the actions in the pharmacovigilance plan and the risk minimisation activities for the individual safety concerns.

Summary of all activities and their milestones:

Art. 123. – (1) This section of the EU-RMP for the medicinal product should be organized in terms of the actions or activities to be undertaken and their milestones.

(2) The reason for this is that one proposed activity (e.g. a prospective safety cohort study) could address more than one of the safety concerns.

(3) Timelines and milestones should be included in the summary with a timetable for the submission of findings.

(4) In developing these milestones one should consider:

a) when it will be possible to detect an adverse reaction with a pre-defined frequency at a pre-defined confidence level; this frequency should be chosen such as to reflect an acceptable level of risk for patients and public health; or

b) when it will be possible to assess with sufficient precision the effect of risk factors associated with the occurence of an adverse reaction;

c) when the results of ongoing or proposed safety studies are expected to be available;

d) The seriousness and magnitude of the risk for which risk minimisation activities are being proposed; evaluation of the effectiveness of the activities will need to be carried out earlier and more frequently if the risk is very serious.

III.14 Submission of updated EU-RMP documents

Art. 124. – (1) As additional information on the safety of a medicinal product becomes available, the safety specification and other sections of the EU-RMP should be updated accordingly.

(2) For example, spontaneous reports, clinical trials and pharmacoepidemiological studies may all give rise to safety signals which need to be investigated or the results from a study could provide new information to update the Safety Specification.

(3) It may be that, based on the new information, it can be concluded that the safety concern has been resolved and that no further actions are needed beyond routine pharmacovigilance; in such cases, additional activities may be proposed and new milestones should be developped.

Art. 125. – This update should include assessment of the effectiveness of the risk minimisation activities within the RMP.

Art. 126. – (1) At each update, consideration should be given as to whether new risk minimisation activities are needed.

(2) This may be because of a new safety concern or with an existing safety concern because the data suggests that the current strategy is not effective.

Art. 127. – Updated EU-RMPs are only required for medicinal products where an EU-RMP (or similar document) has already been submitted under the conditions in chapter III section 4 or required under the terms of the marketing authorisation.

Art. 128. – (1) The updated EU-RMP should be submitted as the same time as the Periodic Safety Update report (PSUR) unless other requirements have been laid down as a condition of the marketing authorisation.

(2) In addition, a new EU-RMP should be submitted:

a) when new information is received that may impact on the current safety specification, Pharmacovigilance plan or risk minimisation activities;

b) within 60 days of an important (pharmacovigilance or risk minimisation) or when a study's results become available;

c) at the request of the NMA.

Art. 129. –A cover letter should be submitted with the updated EU-RMP briefly summarising the changes from the previous EU-RMP.

Art. 130. – (1) Where no changes to any part of the EU-RMP have occured since the last submission, a letter stating this, and the date of the last EU-RMP submission should be sent.

(2) In this circumstance it is not necessary to re-submit the EU-RMP with the letter.

Periodic Safety Update Report

Art. 131. – A summary of any amendments made to the EU-RMP, prior to the data lock point of the Periodic Safety Update Report (PSUR) should be included in the PSUR (see Addendum to ICH-E2C Clinical Safety Data Management. Periodic Safety Update Reports for Marketed Drugs, section 2.8.3. (see Annex 4).

Art. 132. –Methods for risk minimisation are exposed in the table below:

Table III.A: Methods for risk minimisation

Risk minimisation activities can be divided into those where a reduction in risk is achieved primarily through the provision of information and education and those which seek to control the use of medicinal products. When it is obvious that, following a risk minimisation activity, attention should be given to the conduct of this activity during the development phase to see the effectiveness and suitability. When this is done, the outcome should be provided in the risk minimisation plan under the appropriate action.

1. Provision of information

Provision of information to Healthcare Professionals and/or Patients on the specific risks of a medicinal product and the measures on how to reduce them is an essential activity of risk management. This provision of information may be confined to information contained within the Summary of Product Characteristics (SPC) and Package Leaflet (routine risk management) or may be through the use of additional educational material (additional risk management). The need for additional material beyond the Summary of Product Characteristics and Package Leaflet will depend upon the risk and should be considered on a case-by-case basis. Experts in risk communication should be consulted as appropriate.

1.1. Additional Educational Material

The need for additional educational material and the form in which it should be provided will depend upon each specific safety concern. The aim of a specialised educational programme for healthcare professionals and/or patients is to:

a) Enhance understanding of the specific risk(s);
b) Enhance understanding of measures to reduce either the frequency or severity of adverse reactions;
c)Enhance early detection and treatment (if applicable) of an adverse reaction;
d)Enhance patient information, awareness and provide information on the need and use of additional precautions.

The educational programme may include but is not limited to the following materials:

a) Direct Healthcare Professional Communications;
b) Physician's Guide to Prescribing;
c) Pharmacist's Guide to Dispensing/Distribution;
d) Checklists for assessing comprehension, knowledge, attitudes, and/or desired safety behaviours about the risk(s). These should be tailored to the target audience (e.g. physicians, pharmacists or patients);
e) Checklists for actions before prescribing or dispensing;
f) Patient Information Brochures;
g) Specific training programmes.

The choice of media may also need to be considered (written, audio or video) as well as the use of drawing/symbols to improve understanding. For medicinal products where the target population may include a larger proportion of visually impaired patients, the use of Braille or audio media should be given special consideration. Pre-testing materials in the target audience(s) is highly desirable to help ensure good comprehension and acceptance of the communication method and consents. A variety of testing methods such as readability testing, focus groups or surveys could be used.
Specific training programmes may be considered in certain circumstances. However, it is unlikely that prescription/dispensing of the medicinal product can be limited to people who have undertaken such a programme.

The above educational materials should be in strict compliance with the contents of the SPC and the Package Leaflet and must be agreed with the NMA.

2. Legal status of a medicinal product

It is possible that controlling the conditions under which a medicinal product may be made available could reduce the risks associated with its use or misuse. This might be achieved by control of either who may be permitted to prescribe or dispense a medicinal product or by controlling who, or the conditions under which a patient may receive a medicinal product.
When a marketing authorisation is granted, it must include information on any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to Patients. This is commonly referred to as the "legal status of the medicinal product". Typically it includes information on whether or not the medicinal product is subject to medical prescription. It may also restrict where the medicinal product can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist).

For medicinal products only available upon prescription, additional conditions may be imposed by classifying medicines into those available only upon either a restricted medical prescription or a special medical prescription. When considering classification as subject to restricted medical prescription the following factors shall be taken into account:

a) the medicinal product, because of its pharmaceutical characteristics, novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
b) the medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere; or
c) the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment.

In the case of an application for a marketing authorisation submitted in accordance with the centralised procedure, the CHMP is responsible for recommending the legal status to the Commission. Although the use of legal status is not an activity that can be used directly by an Applicant for the purposes of risk reduction, the Applicant could request the NMA to consider a (particular) legal status.

However, the definition of what constitutes a "specialist" is not uniform throughout the Member States so, in practice the provisions of the last indent are usually phrased in section 4.2 of the Summary of Product Characteristics as: "treatment by a physician experienced in the treatment of <the disease>". Although restriction to use in a hospital environment may in practice ensure that the medicinal product is always prescribed by a specialist, this need to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicine can be safely administered. For example the term "clinic" has different connotations depending upon the country. For this reason, the type of equipment needed may be specified rather than a location, e.g. "use in a setting where resuscitation equipment is available."

For classification as subject to special medical prescription the following factors should be taken into account:

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 or 1971; or
- the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes; or
- the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the previous indent as a precautionary measure.

There is possibility of implementing further sub-categories at Member State level which permits the Member States to tailor the broad classifications described above to their national situation. The definitions and the implementation vary in those Member States where the sub-categories exist.

3. Control at pharmacy level

The control of dispensing is another potential activity for risk management. Pharmacists who are well informed about the risks of a medicine can help educate the patient and provide an additional level of protection.

4. Control of prescription size or validity

Limiting a validity of a prescription is another potential activity for risk management in the situation where decision to prescribe depends upon the results of a test which is only valid for a specific time. In some Member States it is possible to limit the validity of a prescription but not in others.

Limiting the number of units prescribed is another risk minimisation activity. This can be useful if regular testing or review is needed. By limiting the number of units, the patient will need to see a Healthcare Professional at defined intervals increasing

the opportunity for testing and reducing the length of time a patient is without review. If this strategy is adopted, it is a pre-requisite that the appropriate pack size is available and that supply issues are addressed. In extreme cases, making units available only in one pack size to try to link prescribing to the need for review may be considered.

A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for medicinal products to get into the general population needs to be controlled.

5. Informed consent and other patient aspects

The patient signs a form to say that he has been given the information, he understands it and agrees to take part in the trial. This is known as „informed consent". A potential activity of risk management would consist of providing adequate information on the risks of the medicinal product and adequate measures in order to minimise them to the patients. Using the „informed consent" outside the framework of the clinical trials is not possible in certain Member States.

6. Restricted Access Programmes

In high-risk situations, it may be necessary to restrict access to a medicinal product to those patients who agree to take part in a specific surveillance programme.

7. Pacient Registries

Patient registries are often suggested as a means of risk management. They have been used (sometimes very successfully) in individual countries to record the results of tests, to ensure that the recommended conditions of use are being adhered to, and control access to the medicinal product. However, there are possible issues about who controls the registry and the confidentiality of medical data.

Whereas patient registries could be a very useful activity for pharmacovigilance studies to characterise risks, their use as a means of controlling access is not currently possible in some Member States. It is strongly suggested that if a Marketing Authorisation Holder is contemplating the use of a patient registry, this should be discussed with the appropriate regulatory authority at a very early stage.

CHAPTER IV

Requirements for Expedited Reporting of Individual Case Safety Reports

IV.1 Introduction

Art. 133. – (1) The obligations of the Marketing Authorisation Holder for recording and reporting suspected adverse reactions associated with a medicinal product for which marketing authorisations are held are defined in Law No. 95/2006, Title XVII – the medicinal product which transposes Directive No. 764/2004/EC.

(2) For suspected adverse reactions requiring expedited reporting, further explanation is provided in this Chapter.

(3) Reporting requirements in special situations, including obligations of the Applicant during the period between submission of the Marketing Authorisation Application and granting of the Marketing Authorisation, are described in Chapter V.

Art. 134. – (1) For authorised medicinal products, independent of the authorisation procedure, adverse reactions received from Healthcare Professionals (physicians), either spontaneously or through post-authorisation studies, should be reported, regardless of whether or not the medicinal product was used in accordance with the SPC.

(2) Adverse reactions identified from the worldwide-published scientific literature should also be reported.

(3) Electronic reporting of adverse reactions is mandatory, save in exceptional circumstances.

Art. 135. – (1) The definitions of „suspected adverse reaction", „serious adverse reaction" and „expected/unexpected adverse reaction" are provided in Annex 1 – Definitions.

(2) In the context of pharmacovigilance, the term „adverse reaction" is considered as synonymous with „suspected adverse reaction" and „adverse drug reaction".

Art. 136. – (1) For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction and therefore should be reported in expedited manner (see Chapter V.9).

(2) In addition, such cases should be considered for reporting as product defects if appropriate (see Compilation of Community Procedures on Inspections and Exchange of Information).

Art. 137. - When a Marketing Authorisation Holder receives an Individual Case Safety Report (ICSR) where the invented name of the medicinal product is not specified but the active substance is included in any of the medicinal products for which a marketing authorisation is held, the Marketing Authorisation Holder should assume that the report may relate to their medicinal product.

Art. 138. - Spontaneous reports of adverse reactions received from Healthcare Professionals should be reported by the MAH if:

- the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to bea t least a causal relationship between the event and the medicinal product;
- the Healthcare Professional has not made any statement on the suspected causal relationship;
- the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility.

Art. 139. - If the Healthcare Professional has made an explicit statement that a causal relationship between the medicinal product and reaction has been excluded and the Marketing Authorisation Holder agrees with this declaration, the event should not be reported.

Art. 140. – (1) When the Marketing Authorisation Holder is aware that a Healthcare Professional may have reported a reaction to one of their medicinal products directly to the NMA of a Member State, the Marketing Authorisation Holder should still report the reaction, informing the NMA that the report may be a duplicate of a previous report.

(2) In this situation, it is essential for the Marketing Authorisation Holder to provide all the available details including all case identification numbers allocated to the case, in order to aid identification of the potential duplicate case.

(3) For further guidance on reporting of potential duplicates, see section A.1.11 „Other case identifiers in previous transmission" of ICH-E2B(M) (see Annex 4).

Art. 141. - The Marketing Authorisation Holder is expected to validate all adverse reactions reported by Healthcare Professionals to ensure, prior to reporting to the NMA, that the minimum information required is included in the report:

a) An identifiable Healthcare Professional reporter (see section A.2 „Primary sources of information" of ICH-E2B(M) (see Annex 4);

- The reporter may be identified by name or initials, address or qualification (e.g. physician, dentist, pharmacist, nurse), according to the EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and national legislation; contact details for a Healthcare Professional should be available for the reporter to be considered as identifiable.

b) An identifiable Patient (see Section B.1 "Patient characteristics" of ICH-E2B(M) (see Annex 4);

- The Patient may be identified by initials, patient number, date of birth, age, age group or sex; the information should be as complete as possible, taking into account EU legislation on data protection (Directive 95/46/EC, Regulation (EC) No 45/2001) and relevant national legislation (see also Chapter III.5, Section 4 of Part III of Eudralex, volume 91 - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

c) At least one suspected medicinal product or active substance (see Section B.4 "Drug(s) information" of ICH-E2B(M) (see Annex 4);

d) At least one suspected adverse reaction (see Section B.2 "Reactions/events of ICH-E2B(M) (see Annex 4).

Art. 142. – (1) Reports should be followed-up to obtain additional information relevant to the case as necessary, and relevant follow-up information should be reported to the NMA (see Chapter III.5, Section 3 of Part III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

(2) All available clinical information relevant to the evaluation of the adverse reaction should be provided (see Chapter III.5, section 3 of Part III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

Art. 143. - For reports on adverse reactions from Patients/Consumers, see Chapter IV, Section 3.5.

Art. 144. - If ICSRs, which do not qualify for expedited reporting as outlined in this Chapter, provide information that may lead to a change in the known risk-benefit balance for the medicinal product, this possible change should be notified to the NMA without delay.

IV.2 Reporting time frames

Art. 145. – (1) The Marketing Authorisation Holder should transmit all ICSRs requiring expedited reporting promptly and no later than 15 calendar days from receipt of the report.

(2) This time frame applies to initial and follow-up information.

Art. 146. – (1) The date the Marketing Authorisation Holder becomes aware of a case which fulfils the minimum information (see Chapter IV, Section 1) should be considered day 0.

(2) The same applies if new information on the case is received by the Marketing Authorisation holder, i.e. the reporting time clock begins again for the submission of the follow-up report from the day the Marketing Authorisation Holder receives relevant follow-up information (see also Chapter III.5, section 3 of Part III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

Art. 147. – The "clock" for expedited reporting "starts" (day 0) as soon as the minimum information (see Chapter IV, section 1) has been brought to the attention of any personnel of the Marketing Authorisation Holder or an organisation having a contractual arrangement with the Marketing Authorisation Holder, including medical representatives.

Art. 148. - For individual cases described in the worldwide scientific literature, "the clock starts" (day 0) with awareness of a publication containing the minimum information (see Chapter I.4, Section 1) by any personnel of the Marketing Authorisation Holder or an organisation having a contractual arrangement with the Marketing Authorisation Holder, including medical representatives. For further guidance see Chapter III.7 of Part III of Eudralex, Volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Art. 149. – (1) Contractual arrangements may be made with a person or organisation to perform literature searches or report relevant individual cases to the NMA.

(2) If another person or organisation is performing these tasks, explicit procedures and detailed agreements should exist between the Marketing Authorisation Holder and this person or organisation to ensure that the Marketing Authorisation Holder is promptly made aware of any individual cases described in the worldwide scientific literature.

Art. 150. – (1) In general, where the Marketing Authorisation Holder has set up contractual arrangements with a person or organisation for the e.g. the marketing of, or research on a medicinal product authorised to this Marketing Authorisation Holder, "the clock starts" as soon as any personnel of the Marketing Authorisation Holder or the other person/organization previously mentioned receives the minimum information that constitutes a reportable case.

(2) Explicit procedures and detailed agreements should exist between the Marketing Authorisation Holder and the person/organisation to ensure that the Marketing Authorisation Holder can comply with his reporting obligations.

IV.3 Requirements by Reporting Source

IV.3.1 Spontaneous Reports from Healthcare Professionals

IV.3.1.1. Individual Case Safety Reports on adverse reactions occuring within the EU

Art. 151. - For all medicinal products, regardless of the authorisation procedure, the Marketing Authorisation Holder should report, on an expedited basis, all serious adverse reactions occuring within the EU, and brought to their attention by Healthcare Professionals, to the Competent Authority of the Member State on whose territory the incident occured (As far as Romania is concerned, the NMA).

Art. 152. - For reporting purposes, any suspected case of transmission via a medicinal product of an infectious agent is considered a serious adverse reaction and therefore should be reported in expedited manner (see Chapter V).

Art. 153. – (1) For medicinal products authorised through the mutual recognition and decentralised procedures, as well as for medicinal products which have been the subject of a referral procedure, the Marketing Authorisation Holder is responsible for ensuring that all serious adverse reactions received from Healthcare Professionals or Competent Authorities within the EU are reported to the Reference Member State.

(2) To avoid duplicate reporting, the Reference Member State/Rapporteur Member State should not retransmit these ICSRs to Eudra Vigilance if they did not occur within its territory (see Chapter II.3 of Part III of Eudralex, volume 9a – Guideline for competent authorities and the Agency).

Art. 154. – (1) Non-serious adverse reactions which occur on the territory of the EU should be reported in an expedited manner only by request from the NMA and, normally, in accordance with provisions of Chapter VI concerning the updated safety-related periodic report.

(2) For centrally authorised medicinal products and their periodic reporting to the EudraVigilance, see Chapter III. 11, section 7 of Part III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

Art. 155. – For an overview on the expedited reporting requirements in Member S tates, see Annexes 6.1.1 and 6.1.2 of Eudralex, volume 9a.

IV.3.1.2.Adverse reactions occuring outside the EU

Art. 156. - For all medicinal products, independent of the authorisation procedure, the MAH should report on the expedited basis, all unexpected and serious adverse reactions and any suspected transmission via a medicinal product of an infectious agent occuring in the territory of a non-EU country, and initially reported/confirmed by a Healthcare Professional, to the EMEA and to all Member States where the medicinal product is authorised.

Art. 157. - Serious unexpected adverse reactions and any suspected transmission via a medicinal product via an infectious agent initialy reported by a Healthcare Professional and subsequently transmitted by a regulatory authority outside the EU to the MAH are also subject to expedited reporting to the Competent Authorities of the EU by the MAH.

Art. 158. – Although not a legal requirement, the Marketing Authorisation Holder is encouraged to also report all expected serious adverse reactions occuring outside the EU on an expedited basis to the EMEA, providing that reporting takes place electronically in accordance with ICH-E2B(M).

Art. 159. - For reporting of non-serious adverse reactions with centrally authorised products and periodic transmission of reports occuring outside the EU to EudraVigilance, see Chapter III.11, section 7 of part III of Eudralex, volume 9a – Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Art. 160. – For an overview on the expediting reporting requirements in Member States, see Annex 6.1.3 of eudralex, volume 9a.

Art. 161. – Reporting requirements on an expedited basis are shown in the table below (highlighted areas in the table refer to situations in which reporting is supported without representing a legal requirement):

MA Type	Origin	Adverse reaction Type	Destination	Dead line
Centralised	EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To MS where adverse reaction occured	15 days
Mutual recognition or decentralised, or when the medicinal product is subject to referral	EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To Member State where adverse reaction occured and to Reference/Rapporteur MS	15 days
National	EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious	To MS where adverse reaction occured	15 days

		agent		
Centralised	Non-EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To EMEA	15 days
National, including mutual recognition, decentralised, or when the medicinal product is subject to referral	Non-EU	All serious unexpected adverse reactions including any suspected transmission via a medicinal product of an infectious agent	To all MSs where the medicinal product is authorised	15 days
National, including mutual recognition, decentralised, or when the medicinal product is subject to referral	Non-EU	All serious adverse reactions, including any suspected transmission via a medicinal product of an infectious agent	To EMEA	15 days

IV.3.2 Reports Published in the worldwide literature

Art. 162. - Individual case reports from the worldwide literature in accordance with the provisions of Chapter IV.1 are considered to be reports of which the Marketing Authorisation Holder can reasonably be expected to be aware and have knowledge of.

Art. 163. – (1) The Marketing Authorisation Holder is therefore expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database (e.g. Medline, Excerpta Medica or Embase) at least once a week in order to have updated information on the medical publications.

(2) Moreover, company offices in each Member State should be aware of publications in their local journals and bring them to the attention of the QPPV as appropriate.

Art. 164. - Cases of adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed to identify individual cases which might qualify for expedited reporting.

Art. 165. - As required by legislation, the Marketing Authorisation Holder should report within 15 days published serious adverse reactions associated with the use of the active substance(s) of their medicinal products, as relevant to the categories identified in Chapter IV, Section 3.1. The procedure for handling of adverse reaction reports published in the worldwide literature is described in Chapter III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Art. 166. - If the medicinal product source and/or the invented name was not specified and ownership of the product cannot be excluded on the basis of the active substance(s), formulation or route of administration, the Marketing Authorisation Holder should assume that it is one of their products the publication refers to, although

the report should indicate that the specific product source and/or the invented name was not identified.

Art. 167. - If multiple medicinal products are mentioned in the publication, reporting should only be made by the Marketing Authorisation Holder(s) of the medicinal product(s) which is (are) identified by the publication's author(s) as having at least a possible causal link associated with the adverse reaction.

IV.3.3 Information on Adverse Reactions from the Internet

Art. 168. – (1) The Marketing Authorisation Holder should regularly screen websites under their management or responsibility, for potential reports on adverse reactions. The Marketing Authorisation Holder is not expected to screen external websites for information on adverse reactions.

(2) However, if a MAH becomes aware of an adverse reaction on any other website, the Marketing Authorisation Holder should review the case and determine whether it should be reported in expedited manner in accordance with Chapter I.4, Sections 3.1 and 3.5.

Art. 169. – (1) The Marketing Authorisation Holder should consider utilising their websites to facilitate adverse reaction collection, e.g. by providing adverse reaction forms for reporting or by providing appropriate contact details for direct communication.

(2) In relation to such reported adverse reactions, identifiability of the reporter and Patient refers to the existence of actual people (see Chapter IV.3.1).

IV.3.4 Reports from Organised Data Collection Systems

Art. 170. - Reporting requirements for cases derived from organised data collection systems (which include clinical trials, post-authorisation studies, registries, post-authorisation named-patient use programmes, other patient support and disease management programmes, surveys of Patients or Healthcare Providers, and information gathering on efficacy or patient compliance) differ depending on whether they are derived from interventional or non-interventional studies.

IV.3.4.1. Interventional Studies

Art. 171. – (1) Interventional studies fall under the provisions of Directive 2001/20/EC transposed into Romania through the Minister of Public Health Order No. 904/2006 and adverse reactions should be reported in line with that Directive and associated guidance, in particular the Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports arising from clinical trials on medicinal products for human use (ENTR/CT3, Volume 10 of the Rules Governing Medicinal Products in the EU, Chapter II), which includes guidance on unblinding, and the Detailed Guidance on the European Database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) (ENTR/CT4, Volume 10 of the Rules Governing Medicinal Products in the EU, Chapter II).

(2) For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter VI.

IV.3.4.2. Non-interventional Studies

Art. 172. – (1) Post-authorisation studies that are non-interventional are not covered by the provisions of Directive 2001/20/EC; these are covered by Directive 2001/83/EC and Regulation (EC) No. 726/2004 (see Minister of Public Health Order No. 904/2006, Chapter IV - definition of a non-interventional trial).

(2) Serious adverse reactions arising from such studies should be reported on an expedited basis according to the same criteria and timelines as adverse reactions reported spontaneously by Healthcare Professionals (see Chapter IV, Section 1); this includes any suspected transmission via a medicinal product of an infectious agent.

(3) For an overview on the expedited reporting requirements in Member States, see Annexes 6.1.1, 6.1.2 and 6.1.3 of Eudralex, volume 9a.

(4) All adverse reactions, also non-serious ones, should be included in the final study report.

(5) For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter VI.

(6) For further information on post-authorisation safety studies see Chapter VII.

IV.3.5 Reports from Patients and Other Costumers

Art. 173. – (1) When the information is received directly from a Patient suggesting that an adverse reaction may have occurred, the Marketing Authorisation Holder should attempt to obtain the Patient's consent to contact the Healthcare Professional involved for further information.

(2) When such a report has been confirmed by the Healthcare Professional, it should be documented as a spontaneous report from a Healthcare Professional and reported according to Chapter IV.

(3) When a Patient submits medical documentation that supports the occurance of the adverse reaction, this information should be considered sufficient to report the individual case if it provides the minimum information (see Chapter IV.1).

(4) For requirements in relation to reporting of outcomes of use of medicinal products during pregnancy, originating from Consumers, see Chapter VI.3.7.

Art. 174. – For requirements in relation to reporting of outcomes of use of medicinal products during pregnancy, originating from Consumers, see Chapter V. 4.

Art. 175. – (1) MSs may have additional requirements in place with regard to reports from Consumers, which need to be followed by the MAH (see Annexes 6.1.1, 6.1.2 and 6.1.3 of Eudralex, Volume 9a).

(2) Adverse reactions which are not medically confirmed should not be reported on an expedited basis to the EMEA/EudraVigilance.

IV.3.6 Reports from other non-medical forces

Art. 176. - If a MAH becomes aware of a case report from non-medical sources other than those mentioned in Chapter IV, section 3.5, e.g. the lay press or other media, every attempt should be made to obtain the minimum information that constitutes an individual case (see Chapter IV, section 1) and to follow-up the case as for reports from a patient (see Chapter IV section 3.5).

IV.4 Data elements for the report

Art. 177. – (1) The principles in the ICH-E2D and ICH-E2B Guidelines should be followed.

(2) Detailed aspects related to the preparation of ICSRs and the applicable data elements are defined in part III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Art. 178. - For the minimum information constituting a case and for the standards relating to the electronic transmission of an ICSR, see Chapter IV section 1 and Chapter III section 2 of Part III of Eudralex, volume 9a – Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

Art. 179. – (1) It is essential for the MAH to provide as many data elements as possible for cases of adverse reactions to facilitate assessment (see Chapter III.5, Sections 1 and 2 of Part III of Eudralex, volume 9a – Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

(2) The MAH is expected to follow-up all reports of serious adverse reactions to their medicinal products to obtain additional information where available.

(3) If the available information does not suffice at the moment of the first report, it must subsequently be provided as follow-up reports (see Chapter IV.1 and Chapter III.5, section 3 of Part III of Eudralex, volume 9a – Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

Art. 180. – (1) The active substance/commercial name of the suspected medicinal product should be reported in accordance with ICH-E2B(M) and according to the provisions in CHAPTER III.5, section 1 of Part III of Eudralex, volume 9a – Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU and Annex 4).

(2) The MAH should transmit the safety-related individual case reports to the competent authorities of the MSs and to the EudraVigilance, in English (see Chapter III.11, section 5 of Part III of Eudralex, volume 9a – Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU).

(3) If necessary, apart from the summary in English, in B.5.1 „Case description, including the clinical conduct, therapeutic measures, result and relevant additional information" of ICH-E2B(M), the Romanian version shall be preserved.

Art. 181. - The MAH may comment on the casual relationship between the suspect medicinal product(s) and the reaction(s) reported and should provide the criteria on which he has made the assessment in field B.4.k.18 „Relatedness of drug to reaction(s)/event(s)" of ICH-E2B(M).

Art. 182. – (1) In situations where ICSRs impact on the known risk-benefit balance of a medicinal product, the MAH should indicate in a separate letter to the NMA and, if applicable, to the EMEA, what action is proposed in relation to the marketing authorisation, the SPC and Patient Information Leaflet.

(2) This should in addition be recorded in field B.5.4. „Sender's comments" of ICH-E2B(M).

IV.5 Method of Reporting

Art. 183. – (1) Electronic reporting of adverse reactions is mandatory, save in exceptional circumstances.

(2) The requirements for electronic transmission of ICSRs to be followed are explained in accordance with Part III of Eudralex, volume 9a - Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU.

CHAPTER V
Requirements for Reporting in Special Situations

V.1 Introduction

Art. 184. – Adverse reactions should be reported according to the requirements outlined in Chapter IV, regardless of whether or not the medicinal products were/were not used in accordance with the authorised Summary of Product Characteristics (SPC) and/or any other conditions laid down for the marketing of the medicinal product.

Art. 185. – In addition to routine expedited and periodic reporting requirements as laid out in Chapters IV and VI, the Marketing Authorisation Holder should be aware of the following additional reporting requirements relating to worldwide experience with the medicinal product:

a) Reporting in the period between the submission of the marketing authorisation application and the granting of a marketing authorisation;

b) Reporting of outcomes of use of a medicinal product during pregnancy;

c) Reporting of paediatric data;

d) Reporting from compassionate/named-patient use;

e) Reporting of lack of efficacy;

f) Reporting of suspected transmission of infectious agents;

g) Reporting in relation to overdose, abuse and misuse;

h) Reporting of medication errors;

V.2 Reporting in the period between the submission of the Marketing Authorisation Application and the Granting of the Marketing Authorisation

Art. 186. – (1) In the period between submission of the marketing authorisation application and the authorisation, information that could impact on the risk-benefit balance may become available to the Applicant (see also Chapter 1, Section 5.1.1 of Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union).

(2) It is the responsibility of the Applicant to ensure that this information is immediately submitted to the NMA or other competent authority in a country where the application is under assessment (including Reference Member State and all Concerned Member States for products assessed under the mutual recognition and decentralised procedures).

(3) For centralised applications, information should also be provided to the EMEA, the Rapporteur and Co-Rapporteur (see Chapter II.3, Section 4.1 and Chapter II.2.A) of Part II of Eudralex, volume 9a – Guideline for the competent authorities and the agency.

V.3 Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons

Art. 187. – (1) Reporting requirements remain following suspension of the marketing authorisation of a medicinal product (see Chapters IV and VI).

(2) Where a marketing authorisation is withdrawn or revoked, the former Marketing Authorisation Holder is encouraged to continue to report in line with Chapter IV to facilitate review of delayed onset adverse reactions and retrospectively notified cases.

(3) It may appropriate to continue submission of PSURs after withdrawal or revocation of the marketing authorisation.

(4) An agreement should be made on a case-by-case basis with the NMA or the EMEA, where applicable.

V.4 Reporting of Outcomes of Use of a Medicinal Product During Pregnancy

Art. 188. – (1) The Marketing Authorisation Holder should follow-up all reports from Healthcare Professionals relating to pregnancies where the foetus may have been exposed to one of his medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure).

(2) Where reports originate from Consumers, reasonable attempts should be made to follow-up via the Patient's Healthcare Professional.

(3) When a Consumer submits medical documentation that supports the occurrence of a suspected adverse reaction, this should be considered sufficient to report the case if it provides the minimum information (see Chapter IV, Section 1).

Art. 189. – When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering the possibility of foetal exposure (i.e. medicinal products taken before conception need to be considered) (see Guideline EMEA/CHMP/313666/2005).

Art. 190. – Individual cases with an abnormal outcome in association with a medicinal product should be reported on an expedited basis, following the reporting requirements outlined in Chapter IV and in accordance with the guideline on exposure to medicinal products during pregnancy: need for post-authorisation data (see Guideline EMEA/CHMP/313666/2005) and the ICH-E2B(M) Guidelines (see Annex 4).

Art. 191. –This refers especially to:

a) Reports of congenital anomalies in the foetus/child;

b) Reports of foetal death and spontaneous abortion; and

c) Reports of adverse reactions in the neonate that are classified as serious.

Art. 192. – Other cases, (i.e. reports of termination of pregnancy without information on congenital malformation and reports of pregnancy exposure without outcome data) should not normally be reported on an expedited basis.

Art. 193. – In certain circumstances, the Marketing Authorisation Holder may be requested to treat any reports of pregnancy exposure as cases requiring expedited reporting (e.g. pregnancy exposure to medicinal products contraindicated in pregnancy because of a high teratogenic potential).

Art. 194. – (1) Information on exposure to medicinal products during pregnancy should include dates of exposure and, as far as possible, details of the period of gestation at the time of exposure, specified by the method of assessment and expressed as weeks and/or days.

(2) This information is necessary to establish a possible causal relationship between the adverse events reported and exposure to the medicinal product.

Art. 195. – (1) It is also important to collect information on pregnancies, which have a normal outcome.

(2) Not infrequently, pregnant women or Healthcare Professionals (Doctors) will contact either the Marketing Authorisation Holder or the NMA requesting information on the teratogenic potential of medicinal products and/or experience of use during pregnancy (see Guideline EMEA/CHMP/313666/2005).

Art. 196. – (1) Expedited reports together with other reports on outcome of exposure during pregnancy should also be included in the Periodic Safety Update Report (PSUR) (see Chapter VI) together with aggregated data on the overall exposure and details of normal/abnormal outcomes.

(2) Reports from prospective registries should also be included and evaluated in the PSUR.

Art. 197. – (1) If, at any time, the Marketing Authorisation Holder identifies, or becomes aware of, a signal of a possible teratogenic effect (e.g. through a cluster of similar abnormal outcomes) all Competent Authorities where a marketing

authorisation is held, and also the NMA and the EMEA in the case of centrally authorised medicinal products, should be informed on an expedited basis.

(2) This provision also applies to possible signals arising from Consumer reports for which medical confirmation has not (yet) been obtained.

V.5 Reporting of Adverse Reactions during Breastfeeding

Art. 198. – Adverse reactions suspected in infants following exposure to a medicinal product from breastfeeding, should be reported in accordance with Chapter IV.

V.6 Reporting on data on exposure of children to medicinal products

Art. 199. – (1) Collection and evaluation of data on exposure of children to medicinal products and associated risks represent an important task and specific guidance is therefore included in the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population (see guideline EMEA/CHMP/PhVWP/235910/2005).

(2) Exposure of children should also be considered and addressed in the Risk Management Plan (see Chapter III).

V.7 Reporting from compassionate/Named-Patient use

Art. 200. – (1) Compassionate or named-patient use of a medicinal product should be strictly controlled by the company responsible for providing the medicinal product and should ideally be the subject of a protocol.

(2) The protocol should ensure that the Patient is registered and adequately informed about the nature of the medicinal product and that both the Physician and the Patient are provided with the available information on the properties of the medicinal product with the aim of maximising the likelihood of safe use.

(3) The protocol should encourage the physician to report any adverse reactions relating to the use of the medicinal product to the NMA, and to the Competent Authority.

Art. 201. – (1) The Marketing Authorisation Holder should continuously monitor the risk-benefit balance of medicinal products used in such circumstances and should respect the adequate reporting regulations to the NMA (subject to protocol or not) and follow the requirements for reporting laid down in Chapter IV.1.

(2) For inclusion of experience acquired from the medicinal product’s use in such conditions, see Chapter VI.

V.8 Reporting of Lack of Efficacy

Art. 202. – (1) Reports of lack of efficacy should not normally be reported on expedited basis, but should be discussed in the relevant Periodic Safety Update Report (see Chapter VI). However, in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes.

(2) Medicinal products used for the threatment of life-threatening diseases, vaccines and contraceptives are examples of classes of medicinal products where lack of efficacy should be considered as cases requiring expedited reporting.

(3) Reportings concerning lack of efficacy should take into account the general context so that it may be established if other cases qualify for reporting.

(4) 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 as cases of lack of efficacy.

(5) However, a life-threatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of a bacterium previous regarded as susceptible should be reported on an expedited basis.

V.9 Reporting of Suspected Transmission of Infectious Agents

Art. 203. – For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction and all similar cases should be reported on an expedited basis to the NMA, according to the criteria shown in Chapter IV, irrespective of whether or not they occur in the EU or elsewhere.

Art. 204. – (1) For cases occurring outside the EU, the legislation includes this reporting requirement specifically to ensure that such cases are appropriately reported and to avoid failure to report due to interpretation of such cases as expected (e.g. given the manufacturing process).

(2) For cases occurring within the EU, the legal requirement to report any such transmission in expedited manner is addressed by the reporting requirements for all (expected and unexpected) serious adverse reactions according to Chapter IV.

(3) For electronic reporting, such cases should to be classified as serious in field A.1.5.1, and field A.1.5.2, "Seriousness Criteria" should be set to "Other medically important condition (see ICH-E2B(M) in Annex 4).

Art. 205. – The requirement to apply MedDRA coding (see Annex 4) is also relevant to the reporting of cases of suspected transmission of an infectious agent.

Art. 206. – Any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

Art. 207. – (1) A transmission of an infectious agent may be suspected from clinical signs or symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product.

(2) As in the case of suspected adverse reactions and adverse reactions, the terms "suspected transmission" and "transmission" are considered synonymous.

(3) Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal products increases the evidence for transmission of an infectious agent.

Art. 208. – Signals arising from case reports on suspected transmission of an infectious agent should be investigated as for other adverse reactions.

Art. 209. – (1) Where a quality defect is suspected or confirmed, the procedures laid down in the Compilation of Community Procedures on Inspections and Exchange of Information should also be followed.

(2) Any contamination of a medicinal product should be considered serious and is likely to be classified as a Class 1 or Class 2 Medicinal Product Defect.

Art. 210. – The poential for transmission of an infectious agent via a medicinal product should also be addressed in the Risk Management Plan (see Chapter III).

Art. 211. – In accordance with provisions of Directive No. 2002/98/EC, transposed in Chapter XI of Law No. 95/2006, Title XVII – The medicinal product, in case of medicinal products derived from human blood or human plasma shall be applied to the hemovigilance procedures.

Art. 212. - Medicinal products should also comply with the Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products, transposed in the Minister of Public Health Order No. 1201/2006.

V.10 Reporting in relation to overdose, abuse and misuse

Art. 213. - (1) The MAH should collect any available information on overdose, abuse and misuse related to his medicinal products.

(2) Reports of overdose, abuse and misuse shouold be routinely followed up to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome.

(3) The MAH should report cases of overdose, abuse and misuse that lead to serious adverse reactions on an expedited basis in accordance with the requirements in Chapter IV.

(4) These provisions include cases of intended suicide.

(5) The MAH should continuously monitor and evaluate the potential impact of overdose, abuse and misuse on the overall risk-benefit balance of the medicinal product.

(6) The potential for overdose, abuse and misuse and the associated risks should also be addressed in the Periodic Safety Update Reports (see chapter VI) and the Risk Management Plan (see Chapter III).

V.11 Reporting of Medication Errors

Art. 214. - (1) The MAH should report cases of medication errors that are associated with serious adverse reactions on an expedited basis in accordance with the requirements in Chapter IV and national provisions.

(2) Cases not associated with adverse reactions and nearly lacking adverse reactions should only be reported in accordance with national requirements.

(3) Cumulative information on medication errors, resulting in adverse reactions or not, should be discussed in the section of the Periodic Safety Update Report on the overall safety evaluation (see Chapter VI).

(4) The potential for medication errors and their prevention should be addressed in the Risk Management Plan (see Chapter III).

Art. 215. - For reporting of medication errors due to confusion of invented names in relation to centrally authorised medicinal products, see the Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed through the ceantralised procedure.

V.12 Reporting in the Event of Public Health Emergencies

Art. 216. - (1) A public health emergency is a public health threat duly recognised either by the World Health Organisation (WHO) or the Community in the framework of Decision No. 2119/98/EC of the European Parliament and of the European Council.

(2) In the event of a public health emergency, regular reporting requirements may be amended.

(3) Such arrangements will be considered on a case-by-case basis and appropriately notified.

CHAPTER VI
Requirements for Periodic Safety Update Reports

VI.1 Introduction

Art. 217. – (1) A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorisation.

(2) At these times, Marketing Authorisation Holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information.

(3) This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorisation and product information.

Art. 218. – (1) Regulation No. 726/2004/EC and and Law 95/2006 establish the periodicity for submission of PSURs unless other requirements are laid down as conditions for the granting of the marketing authorisation.

(2) This Chapter is consistent with ICH-E2C and the Addendum to ICH-E2C (now ICH-E2C(R), see Annex 4).

Art. 219. – It should be noted that electronic periodic submission of Individual Case Safety Reports (ICSRs) for centrally authorised products, described in Chapter III.11, Section 7 under Part III of the Eudralex volume 9A, is a process that is independent of PSUR submission.

Art. 220. – (1) Once a medicinal product is authorised in the EU, even if it is not marketed, the Marketing Authorisation Holder is required to submit PSURs at 6-monthly intervals.

(2) When launch dates are planned, this information should be reflected in the upcoming PSUR.

Art. 221. – (1) Once marketed, 6-monthly PSUR submissions should be continued following initial placing on the market in the EU and until two full years of marketing experience in the EU has been gained.

(2) Then, PSURs should be submitted once a year for the following two years and thereafter at 3-yearly intervals.

Art. 222. – PSURs should also be submitted upon request of the NMA at any time after granting of the marketing authorisation.

Art. 223. – Moreover, review of the periodicity is also part of the RMP and its assessment (see Chapter III).

Art. 224. –There may be situations where exceptionally the submission of 6-monthly and subsequent yearly PSUR may be re-started, or where other amendments of the periodicity are required (see Chapter VI, Section 2.4.3.)

Art. 225. – (1) For medicinal products authorised through the centralised procedure, PSURs should be submitted to the NMA and to the EMEA in accordance with Regulation No. 726/2004/EC, Art. 24.

(2) For medicinal products authorised nationally, PSUR should be submitted to the NMA in accordance with Law 95/2006 (see Distribution Requirements and Address Lists for PSURs, Annex 6.2 of the Eudralex, Volume 9a).

Art. 226. – If the Marketing Authorisation Holder considers, on the basis of the data included in the PSUR, that amendment of the Summary of Product Characteristics (SPC) is necessary, a variation application should be submitted with the PSUR, or where this is not possible, a timetable for submission should be proposed at the time of PSUR submission.

Art. 227. – (1) For medicinal products authorised through the centralised, mutual recognition or decentralised procedure, amendments to the PSUR submission periodicity should be agreed via a type II variation.

(2) For nationally authorised medicinal products, amendments to the PSUR submission periodicity should be agreed according to the national requirements.

Art. 228. – (1) For nationally authorised medicinal products, including those authorised through the mutual recognition or decentralized procedures, initiatives have been taken by the National Competent Authorities to synchronise PSUR submission schedules for products containing the same active substance.

(2) For many active substances, harmonised “virtual” birth dates, so-called EU Harmonised Birth Dates (EU HBDs) and related harmonised data lock points for the following PSURs have been agreed between the relevant Marketing Authorisation Holders for originator products and national Competent Authorities.

(3) These harmonised birth dates and related data lock points are published online, on the site called “the Heads of Medicines Agencies”.

(4) Marketing Authorisation Holders for generic products are highly recommended to use the same PSUR submission schedules as those agreed for the originator medicinal product.

VI.2 General principles

VI.2.1 General scope of information

Art. 229. – (1) The main focus of the PSUR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR.

(2) For this purpose, analysis of adverse reaction reports, an overview of cumulative data, safety data from studies and other relevant safety information, as well as follow-up of any Risk Management Plan (see Chapter I.3) should be adequately addressed in the PSUR.

(3) Reports of lack of efficacy (see Chapter V.8), specifically for medicinal products used in the treatment of life-threatening conditions and for other medicinal products, e.g. contraceptives and vaccines, may represent a significant hazard and therefore may give rise to a safety concern.

(4) These types of cases should be discussed within the PSUR (see Chapter VI.3.9.1).

(5) Moreover, data from pregnancy experience and outcome should also be discussed.

Art. 230. – (1) The increased frequency of Individual Case Safety Reports (ICSRs) for known adverse reactions is considered as relevant new information.

(2) Although increased reporting should also be discussed in the PSUR, it is not possible to provide specific guidance as to what constitutes increased reporting or what ethod should be used for quantifying this.

(3) The Marketing Authorisation Holder should provide details of the methods that have been used.

(4) Judgement should be used in such situations to determine whether the data reflect a meaningful change in occurrence of adverse reactions or in the safety profile and whether an explanation can be proposed for such a change (e.g. population exposed, duration of exposure).

VI.2.2 A single periodic safety report for medicinal products containing an authorised active substance for a single Marketing Authorisation Holder.

Art. 231. –In view of facilitating a consistent and complete examination of the safety information on the active substance(s) in a single document, it is recommended that all the information on all the information, pharmaceutical forms, administration routes and regimens for an active substance pharmacologically contained in authorised medicinal products for a single MAH are included in a single updated safety periodic report having a single deadline for receiving information, common for all the aspects of the medicinal product.

Art. 232. – When relevant and possible, data relating to a particular indication, pharmaceutical form, route of administration or dosing regimen should be presented in separate sections within the body of the PSUR and any safety concerns addressed accordingly without preparing a separate PSUR (e.g. a section dedicated to paediatric use summarising safety as well as exposure information).

Art. 233. – (1) In exceptional cases, the EMEA, the NMA or the Marketing Authorisation Holder may consider it appropriate to have separate PSURs.

(2) In such cases, agreement should be obtained at the time of authorisation or during the post-authorisation phase, as applicable.

(3) Examples include :

a) Medicinal products authorised through line extensions to existing medicinal products (e.g. an active substance in two or more different formulations for systemic versus topical administration) with cross-reference between PSURs, if appropriate (see Chapter VI.2.4.3);

b) Fixed combinations, where options include either a separate PSUR for the combination with cross-reference to the single-substance PSUR(s) or inclusion of the fixed combination data within one of the single-substance PSURs.

Art. 234. – If a subsequent marketing authorisation is granted to a Marketing Authorisation Holder for a medicinal 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 used for the following joint PSURs covering the first and all subsequent medicinal products.

Art. 235. – (1) In addition, in order to put in place measures facilitating work sharing of PSUR assessment among Competent Authorities, harmonisation of birth dates, renewal dates and/or PSUR submission schedules for medicinal products containing the same active substances may be proposed by the Marketing Authorisation Holder or the NMA.

(2) In this context, submission of a type II variation to amend the schedule is not required, if the Marketing Authorisation Holder follows the harmonised PSUR submission schedule.

VI.2.3 Authorised medicinal products for several Marketing Authorisation Holders

Art. 236. – (1) Where a medicinal product is authorised to more than one Marketing Authorisation Holder, in the case of multiple applications, submission of common PSURs is acceptable provided that the medicinal products remain identical in all respects apart from their invented names and that the PSURs are submitted separately by each Marketing Authorisation Holder.

(2) The data lock point should be based on the birth date used for the first authorised product.

(3) The submission cover letter should confirm that the data in these PSURs are identical.

Art. 237. – (1) Generic medicinal products should preferably have the same PSUR submission periodicity as the corresponding originator product (see Chapter VI, Section 2.4.3).

(2) It is generally considered acceptable that Marketing Authorisation Holders for generic medicinal products collaborate on the preparation of PSURs.

(3) However, each Marketing Authorisation Holder remains responsible for the appropriate submission of PSURs for their medicinal products.

(4) Where common PSURs are submitted, the Marketing Authorisation Holders should confirm in writing that the data in these PSURs are identical.

Art. 238. – Marketing Authorisation Holders who have contractual arrangements in place but opt not to submit common PSURs, should ensure that all data which may meaningfully contribute to the safety analysis and influence any proposed or effected changes in the Product Information of the medicinal product authorised to the reporting Marketing Authorisation Holder, should be included, with the source indicated, and discussed in the PSUR, even if it is known that they are included in another Marketing Authorisation Holder's PSUR.

VI.2.4 Frequency of Review and Reporting

VI.2.4.1 Regular and Ad Hoc submission of PSURs

Art. 239. – In accordance with the regular periodicity for PSUR submission, PSURs are required to be prepared and submitted:

- before initial placing on the EU market:
- immediately upon request from the NMA or the EMEA; and
- at least every 6 months after authorisation;
- after initial placing on the EU market:
- 6-monthly PSUR condition should be continued until two full years of marketing experience in the EU has been gained;
- yearly PSURs for the following two years; and
- thereafter PSURs should be submitted at 3-yearly intervals;
- at the first renewal;
- in addition, PSURs should be submitted immediately upon request from the NMA or, for centrally authorised medicinal products, from the EMEA.

Art. 240. – The first PSUR should have a data lock point within 6 months after granting of the marketing authorisation.

Art. 241. – The date of initial placing on the EU market is the date of launch, for the first time, in any Member State.

Art. 242. – Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the data lock point.

Art. 243. – (1) Because the renewal is an independent process, it does not change the data lock point and submission schedule for the PSURs.

(2) It should be noted that re-assessment of the risk-benefit balance at the time of renewal of the Marketing Authorisation is an opportunity to review and, if necessary, change the periodicity PSUR, or to request a second renewal.

Art. 244. – (1) When yearly or 3-yearly PSURs should be submitted, multiple 6-monthly or yearly PSURs are acceptable, accompanied by a Summary Bridging Report, the content of which is described in Chapter VI, Section 4.

(2) It should be noted that in such cases, the Marketing Authorisation Holder should not send 6-monthly or yearly PSURs 60 days after the data lock points of these 6-monthly or yearly PSURs, but should send them only at the required due date (yearly or 3-yearly).

Art. 245. – (1) If a time gap occurs between the data lock point of a regular PSUR and a request from the NMA (e.g. renewal, Risk-Benefit Review, ad hoc PSUR request), a PSUR Addendum Report should also be submitted (see Chapter VI.5).

(2) For a PSUR that spans longer time intervals, e.g. 3 years, an Addendum Report may only be submitted if the time since preparation of the 3-year PSUR and the locally required report is greater than 6 months.

Art. 246. – For PSURs requested for immediate submission by the NMA or the EMEA on an ad hoc basis, the Marketing Authorisation Holder should liaise with the NMA/EMEA to agree the PSUR submission date, depending on the urgency of the issue.

Art. 247. – (1) Exceptionally, a MAH may make a special request to the NMA for 30 additional calendar days to submit a PSUR.

(2) Ideally, this request should be made before the data lock point.

(3) The NMA should respond as rapidly as possible.

(4) The reason for such a request should be justified and could include:

a) a large number of case reports for the reporting period, provided that there is no new significant safety concern;

b) safety concerns raised by the NMA in the previous PSUR for which the Marketing Authorisation Holder is preparing additional or further analysis in the next PSUR; and/or

c) safety concerns identified by the Marketing Authorisation Holder that might require additional or further analysis.

Art. 248. – (1) The Marketing Authorisation Holder should make such a request only for the specific PSUR in question and not for subsequent PSURs.

(2) Subsequent PSURs will generally be expected to be submitted on the appropriate date in line with their original periodicity.

VI.2.4.2 Submission of Periodic Safety Update Reports for Renewal of Marketing Authorisations

Art. 249. – (1) The Guideline on the Processing of MA Renewals in the centralized procedure and the Guideline on the Processing of MA Renewals in the Mutual Recognition and Decentralised Procedures define the different requirements to be respected for the purpose of data submission as part of the renewal application (for

both Guidelines see Volume 2C of The Rules Governing Medicinal Products in the European Union).

Art. 250. – (1) The MAH should submit safety data with the renewal application at least 6 months before the expiry date of the marketing authorisation in the EU.

(2) For the submission of safety data as part of the application for renewal of the marketing authorisation, the PSUR concept should be used.

(3) The Marketing Authorisation Holder should lock the data no more than 60 days before submitting the PSUR.

Art. 251. – (1) The data lock point for submission of safety information should be at 4 years and 4 months following the marketing authorisation date.

(2) Renewal applications may be submitted earlier than 6 months before the expiry date of the marketing authorisation in any Member State, in order to facilitate synchronisation of the PSUR submission schedule as well as harmonisation of renewal dates.

Art. 252. – (1) For the purpose of the renewal application, the Marketing Authorisation Holder should submit the following:

a) the PSUR, or the PSUR plus a PSUR Addendum Report (see Chapter VI, Section 5) or plus line-listings and/or summary tabulations, or only a PSUR Addendum Report, or only line-listings and/or summary tabulations (see Chapter VI.2.4.4 and 2.6.3) covering the period since the data lock point of the last PSUR (e.g. for the first renewal, the safety data of this PSUR or Addendum Report together with the PSURs previously submitted should cover a period of 4 years and 4 months since the marketing authorisation); and

b) a PSUR Summary Bridging Report, bridging all PSURs (including those already submitted) covering the period of 4 years and 4 months; alternatively, the information which corresponds by its content with the PSUR Summary Bridging Report may be included in the Clinical Overview, to be submitted with the renewal application. It is accepted that previously submitted PSURs should not be re-submitted, provided that a list of original submission dates is appended to the Summary Bridging Report.

Art. 253. – (1) If at the time of the first MA renewal, the NMA or the EMEA concludes that an additional renewal is needed, this conclusion may also include a requirement for an additional period of 6-monthly or yearly PSURs.

(2) The second renewal application should discuss PSURs data covering a five-year period since the data lock point of the PSUR(s) submitted with the first renewal application.

Art. 254. – (1) Because the renewal is an independent process, it does not change the periodicity and submission dates for PSURs due as part of pharmacovigilance reporting requirements.

(2) It should be noted that re-assessment of the risk-benefit balance at the time of the MA renewal is an opportunity to review and, if necessary, change the PSUR periodicity, or to request a second MA renewal.

Art. 255. – The MAH should discuss the requirements for PSURs for the MA renewal applications with the relevant Competent Authorities of the Member States and/or the Agency, and agree on the appropriate PSUR documentation required.

VI.2.4.3 Circumstances Where the Periodicity May Be Amended

Art. 256. – (1) Submission of PSURs is part of the normal conditions of marketing authorisations and pharmacovigilance obligations of the Marketing Authorisation Holder.

(2) The periodicity of PSUR submission may be amended, as required by the NMA or proposed by the Marketing Authorisation Holder.

(3) This may result in more or less frequent submission of PSURs.

(4) However, submission of PSURs at a lower frequency than once every 3 years is not possible.

Art. 257. – (1) Where an amendment is proposed, the Applicant/Marketing Authorisation Holder 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.

(2) If a Marketing Authorisation Holder applies for such an amendment following authorisation, such an application should follow the procedures for a type II variation.

Art. 258. – Circumstances where less frequent submission of PSURs may be appropriate include:

a) Medicinal products authorised through line-extensions to an existing medicinal product;

b) Newly authorised generic medicinal products.

Art. 259. – A priori, a line-extension triggers the restart of the regular PSUR periodicity, unless a different periodicity has been agreed as a condition for the granting of the marketing authorisation (Article 816 (6) of Law 95/2006).

Art. 260. – (1) However, in many cases, there will be no need to restart the regular PSUR periodicity following the line-extension, as data for the newly authorised medicinal products may be addressed in the PSURs submitted according to the existing submission schedule.

(2) A justification for continuing the existing submission schedule should be provided by the Marketing Authorisation Holder as part of the line-extension application, and the conditions for the authorisation will include any amendment of the periodicity, if required, as part of the outcome of the application evaluation.

Art. 261. – (1) Where separate PSURs for the product approved through the line-extension are considered appropriate, these should be submitted in accordance with the authorisation date of the newly approved medicinal product by starting the regular PSUR periodicity, while the PSUR submission for the previously authorised medicinal product(s) continues according to the existing submission schedule.

(2) These requirements should be reflected in the conditions for the authorisation.

(3) When separate PSURs are no longer considered necessary, data relevant to the product approved through the line-extension should be incorporated in a single PSUR covering all related medicinal products.

Art. 262. – The addition of a paediatric indication for an already existing medicinal product is an example of a line-extension which would result in re-starting the regular PSUR periodicity following the authorisation date of the newly approved medicinal product (see Guideline EMEA/CHMP/PhVWP/235910/2005).

Art. 263. – (1) For newly authorised generic medicinal products or products authorised on the basis of informed consent applications, application for submission of PSURs on a 3-yearly basis may be included in the authorisation application.

(2) PSURs for such medicinal products should preferably have the same data lock points as the corresponding originator medicinal product (see Chapter VI, Section 2.4.3).

(3) Such applications will be assessed on a case-by-case basis by the NMA.

Art. 264. – (1) Circumstances where more frequent PSUR submission may be required include:

a) variations introducing new indications, populations, dosage forms and routes of administration;

b) an active substance which is a different salt/ester or derivative (with the same basic therapeutic moiety);

c) the presence of an excipient without an established safety profile; and

d) a Risk Management Plan in place for a corresponding originator product requiring specific monitoring of a safety concern.

(2) In some circumstances, e.g. for biological products, a change in the manufacturing process may require close monitoring of possible clinical impact in terms of safety; therefore, the conditions under which the related variation of the marketing authorisation is granted, may include a re-start of the regular PSUR periodicity.

Art. 265. – If the NMA considers it appropriate to amend the PSUR periodicity and submission schedule, this should be clearly communicated to the Marketing Authorisation Holder.

VI.2.4.4. Preparation of Periodic Safety Update Report according to the International Birth Dates

Art. 266. – Medicinal products, which are also authorised outside the EU, will have an International Birth Date (IBD).

Art. 267. – (1) The IBD is the date of a medicinal product granted to the Marketing Authorisation Holder (or a contractual partner of the Marketing Authorisation Holder) anywhere in the world.

(2) For practical reasons, the IBD may be defined as the last day of the month in which this first authorisation date falls.

Art. 268. – The EU Birth Date (EBD) is the date of first marketing authorisation granted for the medicinal product in any EU Member State to the Marketing Authorisation Holder.

Art. 269. – In order to harmonise PSUR submissions internationally, the Marketing Authorisation Holder may use the IBD to determine the dates of the datalock points for the PSUR submission schedule, provided that the first datalock point falls within the 6 months following the EBD within the EU.

Art. 270. – After initial placing of the medicinal product on the EU market, the Marketing Authorisation Holder should submit at least four PSURs covering 6 months each, in order to ensure that two full years of experience with the medicinal product on the EU market are covered through provision of 6-monthly PSURs, while keeping the data lock point according to the IBD or EBD.

Art. 271. – (1) For purely nationally authorised medicinal products that are marketed in Member States, the MAH may wish to synchronise national birth dates with the IBD.

(2) Although such a process may be difficult (e.g. multiple applications for variations might be required), such a step may be feasible and should be discussed with the NMA.

(3) If feasible, this process may be implemented by notification.

Art. 272. – (1) Pentru medicamentele autorizate prin procedură naţională, inclusiv pentru cele autorizate prin procedură de recunoaştere mutuală sau descentralizată, ale căror date naţionale de naştere sunt utilizate pentru stabilirea depunerilor de RPAS, DAPP şi ANM pot desemna o dată europeană armonizată de naştere (vezi CHAPTER VI.1). For nationally authorised medicinal products, including those authorised through the mutual recognition or decentralised procedures, where national birth dates are used to determine the submissions of PSURs, the Marketing Authorisation Holders and Competent Authorities may liaise and designate an EU HBD which may be the IBD (see Chapter I.6, Section 1).

(2) After such harmonisation of the birth date, the first PSUR to be submitted in the EU should be based on the EU HBD and should cover a period in accordance with the life cycle of the product in the EU (6 months, 1 year or 3 years).

(3) When PSURs have previously been submitted in Member States based on different national birth dates, the NMA should accept that there may be an overlap between the last PSUR based on a national birth date and the first PSUR based on the EU HBD.

VI.2.5. Reference Safety Information

Art. 273. – (1) An objective of a PSUR is to establish whether information recorded during the reporting period is in accordance with previous knowledge of the medicinal product’s safety, and to indicate whether changes should be made to the Product Information or the Risk Management Plan.

(2) Reference information is needed to carry out this comparison.

Art. 274. – Having one reference safety document would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report also accepted in other regions of the world.

Art. 275. – (1) It is common practice for Marketing Authorisation Holders to prepare their own Company Core Data Sheets (CCDS) which includes material relating to safety, indications, dosing, pharmacology and other information concerning the medicinal product.

(2) A practical option for the purpose of the PSUR is for each MAH to use, as a reference, the safety information contained within the CDS, which is referred to as Company Core Safety Information (CCSI).

Art. 276. – (1) For the purposes of PSURs, the CCSI forms the basis for determining whether an adverse reaction is already listed or is still unlisted (listed and unlisted are terms that are introduced to distinguish them from the usual terminology of expectedness, which is used in association with the authorised Medicinal Product Information).

(2) The EU Summary of Product Characteristics (SPC) or national SPC authorised by a Member State continues to be the reference document upon which the (un)expectedness is based for the purpose of expedited post-authorisation safety reporting in the EU.

Art. 277. – (1) It is important to highlight meaningful differences between the CCSI and the EU or national SPC in the cover letter accompanying the submission of the PSUR.

(2) The EU or national SPC should also be provided.

Art. 278. – For 6-monthly and yearly PSURs the version of the CCSI in effect at the beginning of the period covered by the PSUR should be used as the reference information.

Art. 279. – However, there may be valid reasons to use the CCSI in effect at the end of the period:

Art. 280. – (1) When producing a PSUR covering a period of more than one year or a PSUR Summary Bridging Report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period.

(2) There may be considerable variation in listedness over the reporting period.

(3) Therefore, the latest CCSI in effect at the end of the period may be used for PSURs covering a longer period.

(4) For PSURs covering a period of more than one year, when listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the version of the CCSI in place at the end of the reporting period as the reference document, as long as that choice is made clear in the PSUR.

Art. 281. – Whether the CCSI valid at the beginning or at the end of the period covered in the PSUR is used, the Marketing Authorisation holder should ensure that all changes to the CCSI made over this period are described in the relevant section of

the PSUR entitled “Changes to the Reference Safety Information” (see Chapter VI, Section 3.5).

Art. 282. – (1) Marketing Authorisation Holders assessing listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any change in listedness assessment over time.

(2) In both cases, changes added since the previous PSUR should be explained in the PSUR sections “Changes to Reference Safety Information” (see Chapter VI, section 3.5) and/or “Overall safety evaluation” (see Chapter IV, section 3.10).

Art. 283. – (1) The Reference Safety Information to be used for PSURs for generic medicinal products base don EU HBD should consist of the common safety information that is included in all current SPCs of the concerned generic medicinal product as authorised in the EU Member States at the time of the data lock point.

(2) In addition, a summary of other safety information that was not included in all SPCs should be submitted.

(3) The MAH should indicate in the PSUR which changes to the Reference Safety Information as used are considered necessary on the basis of the data examined in the PSUR.

VI.2.6. Presentation of Data on Individual Cases

VI.2.6.1 Sources of Information

Art. 284. –Generally, adverse reaction data from the following sources are potentially available to the MAH and should be included in the PSUR:

a) Adverse reaction reports notified directly to the Marketing Authorisation Holder (or under its control):

- Spontaneous reports from Healthcare Professionals;
- Reports from Marketing Authorisation Holder-sponsored studies or named-patient/compassionate use;
- Reports from Patients and other Consumers (not medically confirmed).

b) worldwide literature;

c) Adverse reaction reports received from regulatory authorities worldwide:

- Spontaneous and non-spontaneous reports from Healthcare Professionals;
- Reports from Patients and other Consumers (not medically confirmed).

d) Other sources of data:

- Exchange of reports on adverse reactions in the framework of contractual arrangements (e.g. licensors-licensees agreements);
- Data from special registries;
- Reports from poison control centres;
- Epidemiological databases.

VI.2.6.2 Description of the Adverse Reaction

Art. 285. – The reaction terms used in the PSUR should be in accordance with the MedDRA terminology (see Annex 3).

Art. 286. – Whenever possible, the original reporter's reaction terms should be used to describe the adverse reaction.

Art. 287. – (1) However, when the original reporter's terms are not medically appropriate or meaningful, the MAH should use the best alternative compatible reaction terms for MedDRA to ensure the most accurate representation possible of the original terms.

(2) Under such circumstances, the following should be borne in mind:

a) in order to be able to make it available on request, the „verbatim" information supplied by the original reporter should be kept on file (in the original language and/or as a medically valid english translation, if applicable);

b) In the absence of a diagnosis by the original reporter, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe the case, in addition to presenting the reported individual signs, symptoms and laboratory data;

c) If the MAH disagrees with a diagnosis that is provided by the original reporter, such disagreement may be indicated within the line-listing of cases (see Chapter VI.2.6.3);

d) The 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 original reporter.

Art. 288. – 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, Marketing Authorisation Holder's medical interpretation (identified by asterisk or other means).

VI.2.6.3 Line listings and/or Summary Tabulations

Art. 289. – Depending on their type or source, available adverse reaction cases should be presented as line-listings and/or as summary tabulations (see Table below).

Art. 290. – A line-listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help Competent Authorities identify cases which they may wish to examine more completely by requesting full case reports.

Art. 291. – (1) The Marketing Authorisation Holder should prepare line-listings of consistent structure and content for cases directly reported to him (or under his control), including those from persons and organizations with whom the MAH has contractual arrangements and special registries (see Chapter VI, section 2.6.1) may not be possible without standardization of data elements, or appropriate due to the paucity of information, and may represent unnecessary re-entry/re-processing of such information of such information by the Marketing Authorisation Holder.

(2) This is also available for published cases (usually, well documented; otherwise, they may come up with information resulting from the case surveillance, such as the author of that report).

(3) It is, however, possible that the inclusion of individual cases coming from second or third sources, as well as persons or organisations having contractual arrangements and special registries with the MAH (see Chapter VI.2.6.1) cannot be released without the standardisation of essential data or cannot be appropriate due to lack of information, therefore determining useless re-entries/re-processings of this information to the DAP.

(4) Therefore, in similar situations, summary tabulations or narrative assessments of this data are acceptable.

Art. 292. – (1) In addition to individual case line-listings, summary tabulations of adverse reaction terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview.

(2) Such tabulations should be based on the data in the line-listings (e.g. all serious adverse reaction and all non-serious unlisted adverse reaction), and also on other cases for which line-listings are not requested (e.g. non-serious listed adverse reactions); details are found in Chapters VI.3.7.1 and 3.7.2.

Source	Type of case	Only summary tabulation	Line-listing and summary tabulation
1. Direct reports to MAH			
- spontaneous reporting*, post-authorisation safety studies and other studies	serious non-serious unlisted non-serious listed		yes yes yes
- Compassionate use programmes	serious serious/attributable to medicinal product by investigator or sponsor		** yes yes
2. Literature	serious non-serious unlisted		yes yes
3. Other sources			
- regulatory authorities	serious		yes
- contractual partners***	serious	yes	
- registries	serious	yes	
- poison comtrol centres	serious	yes	
- epidemiological databases	serious	yes	

* Medically unconfirmed reports should be provided as an annex to the PSUR as a line-listing.
** Line-listing should be provided as an annex to the PSUR.
*** For the purpose of this Table, the term contractual partners does not refer to persons and organisations to whom the MAH has transderred pharmacovigilance tasks and functions. These persons and organisations are inluded in "Direct reports to MAH".

VI.3. Model for a Periodic Safety Update Report (PSUR)

Art. 293. – The following Sections are organised as a model PSUR; in each of these Sections, guidance is provided on what should be included.

VI.3.1. PSUR section “Executive Summary”

Art. 294. – (1) The Marketing Authorisation Holder should prepare a brief overview of each PSUR in the form of an Executive Summary to provide the reader with a description of the most important information.

(2) The Executive Summary should be placed at the beginning of the PSUR immediately after the title page and should include the following:

a) The worldwide marketing authorisation status (including a list of countries where the product is authorised/marketed and the authorised indications;

b) Other relevant regulatory information related to the period covered by the PSUR (e.g. any urgent safety restriction should be highlighted);

c) patient exposure data;

d) number of new case reports received during the period covered by the PSUR and the cumulative number;

e) particular issues and safety concerns investigated;

f) Overall findings of the PSUR;

g) conclusions;

Art. 295. – When the MAH has performed a review of one or several specific safety concerns, this should be stated in this Executive Summary (as well as the nature of safety concerns that have been reviewed).

VI.3.2. PSUR section “Introduction”

Art. 296. – The MAH should briefly introduce the medicinal product in this PSUR but is also placed in perspective relative to previous PSURs and circumstances.

Art. 297. – Reference should be made not only to medicinal product(s) covered by the PSUR but also those excluded.

Art. 298. – Exclusions should be explained; for example, they may be covered in a separate PSUR (e.g. for a combination medicinal product).

Art. 299. – If it is known that a PSUR on the same medicinal product(s) will be submitted by another MAH and some of whose data are included in the report (see Chapter VI, section 2.3), the possibility of data duplication should be noted.

VI.3.3. PSUR section “Worldwide Marketing Authorisation Status”

Art. 300. – This section of the PSUR provides cumulative information.

Art. 301. – The following information should be provided for each indication, usually as a table, for all countries where a regulatory decision about marketing has been made related to the following:

a) dates of MA and subsequent renewal (where PSURs are common for identical medicinal products with different invented names, or in the case of generic medicinal products, the list of the dates should cover all medicinal products separately);

b) any qualifications surrounding the marketing authorisation, such as limits on indications if relevant to safety;

c) Treatment indications and special populations covered by the market authorisation, when relevant;

d) lack of approval, including explanation, by worldwide regulatory authorities;

e) withdrawal by the company of an application for authorisation submission if related to safety or efficacy;

f) Dates of launch (where PSURs are common for identical medicinal products with different invented names or in the case of generics, the listing of the dates should cover separately all medicinal products);

g) Dates when the marketing authorisation has been revoked/withdrawn or dates when the marketing or marketing authorisation has been suspended either by a regulatory authority or voluntarily by the MAH;

h) Invented name(s).

Art. 302. – (1) 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 medicinal product is authorised.

(2) However, when there are important differences, which would reflect different types of patient exposure, such information should be noted.

(3) This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures.

Art. 303. – If more convenient and useful, separate regulatory status tables for different medicinal product uses or forms should be utilised.

Art. 304. – Country entries should be listed in chronological order of regulatory authorisations.

Art. 305. – (1) Annex 4 provides an example, with fictitious data for an antibiotic, of how such a table might be organised.

(2) The medicinal product was initially developed as a solid oral dosage form for out-patient treatment of various infections.

VI.3.4. PSUR section "Update of Regulatory Authority or Marketing Authorisation Holder Actions taken for Safety Reasons"

Art. 306. – This section should include details on the following types of worldwide actions relating to safety that were taken during the period covered by the PSUR and between data lock point and PSUR submission:

a) Marketing authorisation withdrawal, revocation or suspension;

b) Failure to obtain a marketing authorisation renewal;

c) Restrictions on distribution;

d) Clinical trial suspension;

e) Dosage modification;

f) Changes in target population or indications;

g) Formulation changes;

h) Urgent safety restrictions.

Art. 307. – (1) The safety-related reasons that led to these actions should be described and documentation appended when appropriate;

(2) Any communication with Healthcare Professionals (e.g. Direct Healthcare Professional Communication (DHPC), commonly called "Dear Doctor Letter" (DDL)) as a result of such action should also be described with copies appended.

(3) For practical reasons, only a single DHPC in the English language, or together with an English summary of the information distributed in one or more countries should be appended.

VI.3.5. PSUR section "Changes to Reference Safety Information"

Art. 308. – (1) For 6-monthly and yearly PSURs, the version of the CCDS with its CCSI coming into effect at the beginning of the period covered by the report should normally be used as the reference information.

(2) For a PSUR covering a period of over one year, the latest CCSI in effect at the end of the period may be used (see Chapter VI, Section 2.5).

Art. 309. – (1) The CCSI used as reference should be numbered, dated and appended to the PSUR and include the date of the last revision.

(2) Changes to the CCSI, such as new contraindications, precautions, adverse reactions or interactions, already made during the period covered by the PSUR, should be clearly described with presentation of the modified sections.

(3) The revised CCSI should be used as the reference for the next PSUR and the next period (see also Chapter VI, Section 2.5).

Art. 310. – (1) With the exception of emergency situations, it may take some time before intended modifications are introduced in the Product Information.

(2) Therefore, during that period the amended reference document (CCSI) may contain more "listed" information than the existing product information in many countries.

Art. 311. – (1) When differences exist between the CCSI and the EU/Member State's Summary of Product Characteristics (SPC) (or the official data sheets/Product Information documents approved in a country), a brief comment should be prepared by the MAH, describing the local differences and their consequences during on the overall safety evaluation and on the actions proposed or initiated.

(2) This commentary may be provided in the cover letter accompanying the local submission of the PSUR.

VI.3.6. PSUR section "Patient Exposure"

Art. 312. – (1) Estimating patient exposure data for marketed medicinal products often relies on gross approximations of in-house or purchased sales data or volume to determine patient exposure.

(2) This is not always reliable or available for all medicinal products.

(3) For example, hospital-based (in-patient exposure) data from the major monitoring sources are frequently unavailable.

(4) It may also be difficult to obtain accurate data for medicinal products of which generic presentations are in use.

(5) For non-prescription medicinal products, use is often on an as-required basis, and individual packages are frequently used by multiple family members of different ages and weights.

Art. 313. – (1) Where possible, an estimate of patient exposure should cover the same period as the interim safety data.

(2) 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.

(3) An explanation and justification should be presented if the number of patients is impossible to estimate.

(4) 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.

(5) Given the difficulty of estimating cases, patient exposure should preferably be provided as person-time of exposure (days, months, years).

(6) The Marketing Authorisation Holder should be consistent in its method of calculation across PSURs for the same medicinal product.

(7) If a change in the method is appropriate, then both methods and calculations should be shown in the PSUR introducing the change.

(8) If these or other more precise measures are not available, bulk sales (tonnage) may be used.

(9) The concept of a Defined Daily Dose may be used in arriving at patient exposure estimates.

(10) When possible and relevant, data broken down by sex and age (especially paediatric vs adult population) should be provided.

(11) Paediatric population exposure should be broken down according to age groups.

(12) An estimate of use outside the terms of the marketing authorisation should be provided along with the method used to provide the estimate.

(13) Pregnancy exposure should also be estimated specially in the case of pregnancy registries using the same data lock point as the PSUR.

Art. 314. – When an observed pattern of case reports indicates a potential problem, details by country (with locally recommended daily dose) or other breakdowns (e.g. indication, dosage form) should be presented if available.

Art. 315. – (1) When adverse reaction data from clinical studies are included in the PSUR, the relevant denominator should be provided.

(2) For ongoing and/or blinded studies, an estimation of patient exposure may be made.

Art. 316. – (1) When exposure data are based on information from a period that does not fully cover the period of the PSUR, the Marketing Authorisation Holder may extrapolate using the available data.

(2) If this it done, it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g. stable sales over a long period of time, seasonality of use of the medicinal product).

Art. 317. – (1) In a PSUR Summary Bridging Report, exposure should be presented including the full reporting period and explaining any differences in this estimation from the simple sum of exposure estimates included in the separate PSURs covered by the PSUR Summary Bridging Report.

(2) In addition, cumulative exposure estimates should be presented (for further guidance see explanations provided in the Risk Management Plan Template in document EMEA/20732/2007).

VI.3.7 PSUR section "Presentation of Individual Case Histories"

Art. 318. – This section should contain a description and analysis of selected cases containing new or relevant safety information and grouped preferably by medically relevant headings/MedDRA System Organ Classes (SOCs).

Art. 319. – A description of the criteria used to select cases for presentation should be provided.

Art. 320. – (1) Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR.

(2) If such information is relevant to the interpretation of the case (e.g. significant impact on the case description or analysis), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.

(3) Cases where follow-up information is not considered to have any impact on the overall assessment of the case and has not lead to relevant coding changes for the case, do not need to be discussed in the body text of the PSUR.

Art. 321. – However, such cases should always be presented in cumulative tables and analysis if relevant.

Art. 322. – With regard to the literature, MAHs should monitor standards, recognized 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.

Art. 323. – Published cases received from other sources (e.g. spontaneous reporting, studies) should only be included once and literature citation should be provided regardless of the "primary" source.

Art. 324. – With regards to spontaneous reports that originate from Patients/Consumers, Marketing Authorisation Holders should:

a) ensure review of data from Patients/Consumers or other non-healthcare professionals;

b) include analysis of this data if associated with a safety concern in the PSUR section "Overall Safety Evaluation" (clearly identifying such reports by their source); and

c) provide the data as a line-listing and summary tabulations (if considered appropriate).

VI.3.7.1 "Cases Presented as Line-Listings"

Art. 325. – (1) The types of cases referenced below should be included in the line-listing.

(2) Attempts should be made to avoid duplicate reporting of cases from literature and regulatory sources.

a) All serious adverse reactions and non-serious unlisted adverse reactions from spontaneous reporting;

b) All serious adverse reactions (attributable to the medicinal product by either investigator investigator or sponsor) available from post-authorisation safety studies (PASS) and other studies (including those which are part of the Risk Management Plan) or named-patient/compassionate use;

c) All serious adverse reactions, and non-serious unlisted adverse reactions from the literature;

d) All serious adverse reactions transmitted to the Marketing Authorisation Holder by worldwide regulatory authorities.

Art. 326. – In addition, the types of cases referenced below should be included as line-listings in the form of an annex to the PSUR:

a) All non-serious listed adverse reactions from spontaneous reporting;

b) All serious and non-serious (listed and unlisted) adverse reactions reported by Patients/Consumers and other non-healthcare professionals (not medically confirmed).

Art. 327. – Suspected transmission via a medicinal product of any infectious agent should be considered as a serious adverse reaction (see Chapter V, Section 9).

Art. 328. – (1) Line-listing (see Annex 5 for Template) should include include each patient only once regardless of how many adverse reaction terms are reported for the case.

(2) If there is more than one reaction, they should all be mentioned but the case should be listed according to the most serious adverse reactions (sign, symptom or diagnosis), as judged by the Marketing Authorisation Holder.

Art. 329. – (1) It is possible that the same Patient may experience different adverse reactions on different occasions (e.g. weeks apart during a clinical trial).

(2) Such experiences should be treated as separate reports.

(3) 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.

(4) Line-Listings should be organised (tabulated) by body system (MedDRA System Organ Classes (SOCs)).

Art. 330. - Where common PSURs are submitted, the line-listings should still reflect the invented name of the medicinal product (or the active substance name if the

invented name of the medicinal products is not available) as reported by the original reporter.

Art. 331. - The following headings should usually be included in the line-listings (see Annex 5):

a) MAH case reference number;

b) country in which the case occured;

c) Source (e.g. clinical trial, literature, spontaneous, regulatory authority);

d) Age and sex of the Patient;

e) Daily dose of the suspected medicinal product (and, when relevant, dosage form or route of administration);

f) Date of onset of the adverse reaction(if not available, best estimate of time to onset from therapy initiation); for adverse reactions known to occur after cessation of therapy, estimate of time lag if possible;

g) Dates of treatment; if not available, best estimate of treatment duration;

h) Description of adverse reaction(s) as reported, and when necessary as interpreted by the Marketing Authorisation Holder (English translation when necessary) (see Chapter VI, Section 2.6.2);

i) Patient outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown). This should indicate the consequences of the adverse reaction(s) for the Patient, using the worst of the different outcomes for multiple reactions;

j) Comments, if relevant (e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medication suspected to play a role in the reactions directly or by interaction; indication treated with suspect medicinal product(s); dechallenge/rechallenge results if available); it should be used only for information that helps to clarify individual cases.

Art. 332. - Depending on the medicinal 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.

VI.3.7.2 “Cases Presented as Summary Tabulations”

Art. 333. – (1) An aggregate summary of each of the line-listing should usually be presented.

(2) These tabulations usually contain more terms than patients.

(3) 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 Annex 6 for a sample data presentation on serious adverse reactions).

Art. 334. – The terms used in these tables should ordinarily be those used by the Marketing Authorisation Holder to describe the case (see Chapter VI, Section 2.6.2).

Art. 335. – (1) Data on serious reactions from other sources (see Chapter VI.2.6.1) should normally be presented as summary tabulations.

(2) If useful, the tabulations may, for example, be sorted by source of information or country.

Art. 336. - 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.

Art. 337. – (1) As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they were derived.

(2) However, for adverse reactions 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.

VI.3.7.3 "Marketing Authorisation Holder's Analysis of Individual Case Histories"

Art. 338. – (1) This section may be used for brief comments on the data concerning individual cases; for example, discussion may be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.).

(2) The focus here should be on individual case discussion and should not be confused with the global assessment in the PSUR section „Overall Safety Evaluation" (see Chapter VI, section 3.10).

VI.3.8 PSUR section "Studies"

Art. 339. – (1) All studies (non-clinical, clinical and epidemiological) yielding safety information (this includes lack of efficacy data) with a potential impact on product information, studies specifically planned, in progress and those published that address safety concerns should be included with a discussion of any interim or final results.

(2) The MAH should not routinely describe all the studies.

(3) Studies that are part of the Risk Management Plan should be mentioned (see Chapter VI, section 3.9.3).

VI.3.8.1 „Newly Analysed Studies"

Art. 340. – (1) 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.

(2) Reference should be made to the Risk Management Plan, where applicable.

(3) 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.

(4) Copies of full study reports should be appended, e.g. in post-authorisation safety studies and for other studies with a significant safety finding only if deemed appropriate.

VI.3.8.2 "Targeted New Safety Studies"

Art. 341. - New studies specifically planned or conducted to examine a safety concern (real or hypothetical) should be described (e.g. objective, starting date, projected completion date, number of subjects, protocol summary).

Art. 342. – (1) When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented.

(2) When the study is completed and analysed, the final results should be presented in a subsequent PSUR as described in Chapter VI.3.8.1.

Art. 343. – Copies of full reports should be appended in the case of post-autorisation safety studies and for other studies with a significant safety finding only if deemed appropriate.

Art. 344. – Planned studies should be discussed in the Risk Management Plan (see Chapter III) and if relevant in the related PSUR section (see Chapter Vi, section 3.9.3).

VI.3.8.3 „Published Studies"

Art. 345. – Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarized and the bibliography provided.

VI.3.8.4 "Other Studies"

Art. 346. – The MAH should provide any relevant information coming from the data collected from pregnancy exposure registries and comment son the positive or negative experience of that medicinal product's use during pregnancy.

VI.3.9 Section „Other Information" of the PSUR

VI.3.9.1 Efficacy-related Information

Art. 347. - For a medicinal product used in prevention (e.g. vaccines) or in treatment in serious or life-threatening diseases (e.g. antibiotics and antiviral products) or medicinal products used in healthy Consumers (e.g. contraceptives), medically relevant lack of efficacy reports, which may represent a significant hazard, should be described and explained.

Art. 348. – When appropriate, all other medically relevant reports of lack of efficacy should be discussed in this section.

VI.3.9.2 Late-breaking Information"

Art. 349. – (1) Any important, new information received after the database was frozen for review and report preparation should be presented in this section.

(2) Examples include significant new cases or important follow-up data.

(3) These new data should be taken into account in the PSUR section "Overall Safety Evaluation" (see Chapter VI, section 3.10).

VI.3.9.3 „Risk Management Plan"

Art. 350. – (1) When a specific Risk Management Plan is in place, it should be discussed.

(2) In this case, the status of the Risk Management Plan and its amendments prior to the data lock point should be presented together with all available study results.

Art. 351. – The assessment of the effectiveness of the risk management system should be presented (see Chapter III).

VI.3.9.4 „Risk-Benefit Analysis Report”

Art. 352. – When a more comprehensive safety or risk-benefit analysis (e.g. all indications reviewed) has been conducted separately, a summary of the analysis should be included in this section.

VI.3.10 PSUR section “Overall Safety Evaluation”

Art. 353. – (1) The MAH should provide a concise analysis of the data presented, taking into account any late-breaking information (see Chapter VI, section 3.9.2) and followed by the MAH’s assessment of the significance of data collected during the period.

(2) Discussion and analysis of the „Overall Safety Evaluation” should be organised by SOC rather than by listedness/seriousness; the latter properties should still be covered under each SOC.

(3) Although related terms may be found in different SOCs, they should be reviewed together for clinical relevance.

Art. 354. – Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases.

Art. 355. – The MAH should also review the cumulative experience and highlight any new information on:

a) a change in characteristics of listed reactions (e.g. severity, outcome, target population);

b) serious unlisted adverse reactions, placing into perspective the cumulative reports;

c) non-serious unlisted adverse reactions;

d) an increased reporting frequency of listed adverse reactions, including comments on whether it is believed the data reflect a meaningful change in adverse reactions occurence.

Art. 356. – This section should also explicitly address any new safety concern on the following (lack of significant new information should be mentioned for each aspect) :

a) medicinal interactions;

b) experience with overdose, deliberate or accidental, and its treatment;

c) abuse or misuse of medicinal products;

d) positive or negative experiences during pregnancy or lactation;

e) experience in special patient groups (e.g. children, elderly, organ impaired, a qualitative description of off-label use should be given);

f) effects of long-term treatment;

g) Patient/Consumer and other non-healthcare professional reports (see Chapter VI, Section 3.7), if appropriate;

h) prescription errors/medication errors, including those associated with invented names or withthe presentation of the medicinal products, that have safety implications, if available.

Art. 357. – (1) A subsection of the PSUR should deal with use of the medicinal product in children if the product has a paediatric indication, if there is evidence of significant off-label use in children or if there are adverse reactions reported in the paediatric population.

(2) Data from completed or ongoing clinical trials should be presented separately from spontaneous reports (see guideline EMEA/CHMP/PhVWP/235910/2005).

VI.3.11 PSUR section „Conclusion"

Art. 358. - The „Conclusion" should address the overall risk-benefit balance in the context of the data presented in the PSUR and:

a) indicate which safety data are not in accordance with previous cumulative experience and the reference safety information (CCSI);

b) specify and justify any action recommended or initiated.

Art. 359. – The need to amend the SPC should be addressed in the cover letter from the MAH, where consistency between the CCSI and the SPC is cross-checked and any comment or planned action is proposed.

Art. 360. – Having made a decision to amend the SPC, the Marketing Authorisation Holder should submit a variation application at the same time as the PSUR or, where this is not possible, state a proposed timetable for submission.

VI.4 Contents of the PSUR Summary Bridging Report

Art. 361. - (1) The PSUR Summary Bridging Report should not contain any new data but should provide a brief summary bridging two or more PSURs, or PSURs and PSUR Addendum Reports (e.g. two consecutive 6-monthly PSUR for a yearly PSUR or six consecutive 6-monthly PSURs to compile 3-year PSUR data.).

(2) It is intended to assist Competent Authorities with a helpful overview of the appended PSURs.

(3) The PSUR data should not be repeated but cross-referenced to individual PSURs.

(4) The format of the Summary Bridge Report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs to which it refers.

Art. 362. - The Summary Bridging Report should contain the following:

a) introduction (a brief description of the purpose of the document specifying the time periods covered and cross-referencing any appended PSURs);

b) worldwide marketing authorisation status (number of countries which have approved the medicinal product);

c) update on regulatory authority or MAH-initiated actions for safety reasons (an integrated summary of actions taken if appropriate);

d) changes to the CCSI (significant changes over the entire period);

e) exposure data (estimation of the total number of patients exposed in the time period);

f) Individual case histories (brief statement outlining the total number of cases presented in the series of PSURs). When there is a specific safety concern that has not been adequately discussed in one or more PSURs, it is considered appropriate to include a cumulative line-listing or summary tabulation for the types of cases of concern presenting adverse reactions ordered by SOC, seriousness and listedness/unlistedness covering the period of the Summary Bridging Report and pointing out any differences from prior listings or tabulations. In this case, there should be a clear understanding that the tables should be generated from a live database, which changes over time as cases are updated. These tables should then reflect the most up-to-date data available at the time they are generated. It is recognised that the case counts in these summary tables may differ somewhat from the contens of the individual tables in the appended PSURs. A general statement describing the differences should be provided;

g) studies (a brief summary of important targeted clinical safety studies);

h) other information (only highly significant safety information received after the data lock point);

i) overview of the safety concerns and Conclusion (unresolved key issues).

Art. 363. – In addition, the cover letter accompanying the Summary Bridging Report should also contain information highlighting any significant differences between the approved SPC and the current CCSI.

VI.5 Contents of the PSUR Addendum Report

Art. 364. – (1) A PSUR Addendum Report is an update to the most recently completed PSUR when a Competent Authority requests or requires a safety update outside the usual IBD-based PSUR submission schedule.

(2) An Addendum Report should be provided when more than 3 months for a 6-monthly or yearly PSUR, and more than 6 months for a PSUR covering a longer period have elapsed since the data lock point of the most recent PSUR.

(3) It may also be appropriate to provide an Addendum Report to the PSUR Summary Bridging Report (see Chapter VI.4).

Art. 365. – (1) The Addendum Report should summarise the safety data received between the data lock point of the most recent PSUR and the NMA’s requested cut-off date.

(2) It is not intended that the Addendum Report should provide an in-depth analysis of the additional cases, as these should be included in the next regularly scheduled PSUR.

(3) Depending on the circumstances and the volume of additional data since the last scheduled report, an Addendum Report may follow the PSUR format or a simplified presentation.

Art. 366. – The proposed simplified presentation should include the following sections, containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

a) Introduction (purpose, cross-reference to most recent PSUR);

b) Changes to the CCSI (including a copy of the most recent CCSI document if it differs from the one in the PSUR);

c) significant worldwide regulatory authorities' actions relevant to safety;

d) Line-listing(s) and/or summary tabulations;

e) Conclusions (brief overview).

CHAPTER VII

Company-Sponsored Post-Authorisation Safety Studies

VII.1 Introduction

Art. 367. – (1) There is a continuous need to monitor the safety of medicinal products as they are used in clinical practice.

(2) Spontaneous reporting schemes provide important early signals of safety concerns and also provide a means of continuous surveillance.

(3) Formal studies to evaluate safety may also be necessary, particularly in the confirmation, characterisation and quantification of safety concerns identified at an earlier stage of product development or during post-authorisation use (see Chapter VIII).

(4) Such studies may also be useful in identifying previously unsuspected adverse reactions or in confirming the safety profile of a medicinal product under normal conditions of use.

(5) In accordance with legal requirements, post-authorisation safety studies (PASS) may be required by the NMA either as a commitment at the time of authorisation or in the post-authorisation phase to further assess a signal.

(6) In either case, such studies will be considered as a relevant part of the Risk Management Plan (see Chapter III).

Art. 368. – (1) This Chapter of Volume 9A applies to the conduct of studies sponsored by the pharmaceutical industry, which evaluate the safety of medicinal products with a marketing authorisation for human use.

(2) They encompass all studies carried out to evaluate the safety of authorised medicinal products and for which a Marketing Authorisation Holder takes responsibility for their initiation, management and/or financing.

(3) This chapter includes studies where the medicinal product is provided by the Marketing Authorisation Holder and those where it is prescribed in the normal way, both in general practice and in the hospital setting.

(4) A study follows a protocol, which defines the study population and the design for its conduct and analysis.

(5) Therefore, in this context, databases searches to count e.g. number of adverse events or number of prescriptions are not considered studies.

Art. 369. – (1) The present guidance provides a framework whereby a variety of data collection methods may be used to evaluate the safety of authorised medicinal products.

(2) Whilst it is recognised that the study design used needs to be tailored to particular medicinal products and safety concerns, this guidance defines the essential principles to be applied in a variety of situations.

(3) Due to the fact that the study methods in this field continue to develop, there will be a need to regularly review guidance to ensure that it reflects advances made in the assessment of product safety (see table VII at the end of this Chapter).

Art. 370. – (1) A post-authorisation safety study is defined in Article 695 (14) of Law 95/2006 as "pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of marketing authorisation, conducting with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product".

(2) According to Art. 21 (c) of Minister of Public Health Order No. 904/2006 on the approval of Norms concerning the implementation of good clinical practice rules carried out on a medicinal product for human use, non-interventional studies are studies „within which the medicinal product(s) are usually prescribed in accordance with the marketing authorisation terms; using in a patient given therapeutic strategies is not previously established via a study protocol, but it is done in accordance with the current practice, while the decision to prescribe the medicinal product is clearly separated from that of including the patient in the study; no additional diagnostic or surveillance procedure shall be applied to patients, while epidemiological methods are used for the analysis of gathered data."

Art. 371. – (1) In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice.

(2) Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies.

(3) The latter are considered clinical trials falling under the scope of the Minister of Public Health Order No. 904/2006.

Art. 372. – (1) If the definition of non-interventional is not met, the study should be considered as interventional.

(2) For instance, studies exploring new indications, new routes of administration or new combinations, after a product has been authorised, should be considered as interventional.

(3) In such cases, Minister of Public Health Order No. 904/2006 and the related guidance should be followed (see Volume 10 of the Rules Governing Medicinal Products in the European Union); the guidance on Good Clinical Practice does not apply to non-interventional post-authorisation studies.

Art. 373. – The guidance below relates principally to those non-interventional post-authorisation studies where there are known safety issues under investigation and/or where the numbers of patients to be included in the study will add significantly to the existing safety data for the medicinal product(s).

Art. 374. – (1) A safety concern may be unexpectedly identified in the course of performing a study on an authorised medicinal product that would normally fall outside the scope of this guidance.

(2) In such cases, the Marketing Authorisation Holder and specifically the QPPV are expected to inform the NMA immediately and to provide a brief report on progress at intervals and at study end as requested by the Authorities.

Art. 375. – If there is doubt as to whether or not a study comes under the scope of the present guidance, the company should discuss the intended protocol with the relevant Competent Authorities of the Member State(s) in which the study is to be conducted (see Chapter VII, section 4.1).

Art. 376. – In addition to the guidance below, MAHs should consider the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE).

VII.2 Objectives of Post-Authorisation Safety Studies

Art. 377. – (1) Post-authorisation safety studies may be conducted for the purpose of identifying previously unrecognised safety concerns (aiming for hypothesis-generation), investigating potential and identified risks (aiming for hypothesis-testing in order to substantiate a causal association), or confirming the known safety profile of a medicinal product under normal conditions of use.

(2) They may also be conducted to quantify established adverse reactions and to identify risk factors.

Art. 378. – Situations where studies may be appropriate include:

a) a medicinal product with a novel chemical structure or novel mode of action;

b) where there is uncertainty as to the clinical relevance of a toxic effect in animals;

c) where there is uncertainty as to the safety profile;

d) where there is a need to better quantify adverse events identified in clinical trials and elucidate risk factors;

e) where there is a need to confirm or refute safety concerns suggested by other sources (e.g. spontaneous reporting);

f) where there is a concern regarding the use of the medicinal product (e.g. to quantify the off-label use); and

g) when there is a need to evaluate the effectiveness of a risk minimisation measure.

Art. 379. – (1) A variety of designs may be appropriate including observational cohort studies, case-control studies or registries (see Table VII.A).

(2) Clinical trials involving systematic allocation of treatment (e.g. randomisation) may also be used to evaluate the safety of authorised products.

(3) Such clinical trials should comply with the requirements of Minister of Public Health Order No. 904/2006.

Art. 380. – (1) The design to be used will depend on the objectives of the study, which must be clearly defined in the protocol and explicitly addressed by the proposed methods.

(2) A reference to the Risk Management Plan should be made in the protocol when such a Plan exists.

(3) In case there is a risk management plan, the protocol should stick to it.

(4) For protocol development consideration should be given to the elements described in Table VII.B at the end of this Chapter.

VII.3 Responsibilities for the Conduct of Post-Autorisation Safety Studies

Art. 381. – (1) The Marketing Authorisation Holder who initiates, manages and/or finances the study is responsible for its conduct and should meet the pharmacovigilance obligations concerning PASS.

(2) The study should be supervised by a designated monitor(s) whose name(s) should be recorded in the study documents.

(3) In case the Marketing Authorisation Holder does not directly conduct the study, detailed and clear contractual agreements for meeting pharmacovigilance obligations should be documented (see Chapter II.3).

Art. 382. The QPPV at EU level and/or, where applicable, the nominated person responsible for pharmacovigilance at national level, should be involved in the review of protocols for all post-authorisation safety studies, in order to ensure compliance with pharmacovigilance requirements.

VII.4 Liaison with Competent Authorities

VII.4.1 Evaluation of the Protocol

Art. 383. – (1) Marketing Authorisation Holders proposing to perform a post-authorisation safety study should send the protocol to the Competent Authority of the Member State(s) in whose territory the study is to be performed.

(2) In case of medicinal products authorised through the mutual recognition or decentralised procedures, the protocol should also be sent to the Reference Member State; in case of centrally authorised medicinal products, this should be sent to the EMEA, the Rapporteur and Co-Rapporteur.

(3) National legal requirements or guidelines should be taken into account in those Member States where these exist, and provisions of Minister of Public Health Order No. 904/2006 should be followed when the study qualifies as a clinical trial.

Art. 384. – Two different situations can be envisaged depending on whether or not the study has been requested by the Competent Authorities:

VII.4.1.1 Studies required by Competent Authorities

Art. 385. – The contact point will depend on the procedure by which the medicinal product has been authorised in the EU:

a) For centrally authorised medicinal products, the EMEA will normally be the contact point. The (Co-)Rapporteur will initially review the draft protocol for approval by the CHMP. The draft protocol may also be discussed at PhVWP level if so requested by CHMP.

b) For medicinal products authorised through the mutual recognition or decentralised procedure, the Reference Member State will normally be the contact point and the initial reviewer of the draft protocol. A further discussion may take place at PhVWP level.

c) For nationally authorised medicinal products, the Competent Authority of the Member State requesting the study and the Competent Authority of each Member State where the study is to be conducted will be the contact points. However, when the need for the study has been discussed at PhVWP level, a Lead Member State may be nominated who will act as the contact point and initial reviewer for the draft protocol. Further discussions may take place at PhVWP level when the study is to be conducted in several Member States or the medicinal product is used in several Member States.

Art. 386. – (1) Meetings will be organised as appropriate between the designated (Co-) Rapporteur or Reference/Lead Member State and the Marketing Authorisation Holder in order to agree upon a protocol and a timetable.

(2) When the Marketing Authorisation Holder considers that the protocol requires a major amendment, this should be reported to the (Co-)Rapporteur or Reference/Lead Member State who will consider its appropriateness and the need for further evaluation at CHMP and/or PhVWP level.

(3) Refinements of exposure and/or case definitions will normally not require notification.

Art. 387. – When the same or a similar study is also requested by other Competent Authorities, e.g. countries outside the EU for centrally authorised or other Member States for nationally authorised medicinal products, an effort should be made by the MAH to reach agreement on a common protocol.

VII.4.1.2 Studies performed at Marketing Authorisation Holder's initiative

Art. 388. – (1) When the study has commenced, the Marketing Authorisation Holder should inform the relevant Competent Authorities of all Member States where the study is being conducted, as well as the EMEA and (Co-)Rapporteur for centrally authorised products and the Reference Member States for medicinal products authorised through the mutual recognition or decentralized procedures.

(2) Any major amendment to the protocol should be reported to the relevant Authorities accompanied by a justification for it.

(3) Refinements of exposure and/or case definitions will normally not require notification.

VII.4.2 Reporting of Adverse Reactions

Art. 389. – (1) For post-authorisation safety studies that qualify as clinical trials, the reporting criteria laid down in Minister of Public Health Order No. 904/2006 and related guidance (see Volume 10 of the Rules Governing Medicinal Products in the EU) should be followed as well as the requirements established for Periodic Safety Update Reports (PSURs) (see Chapter VI).

Art. 390. – For non-interventional post-authorisation safety studies, conducted inside and outside the EU, the usual regulatory requirements for reporting of adverse reactions should be fulfilled according to Chapters IV and VI (in conjunction with Part III of Eudralex, Volume 9a – Guideline for Marketing Authorisation Holders, Competent Authorities and EMEA for electronic exchange of pharmacovigilance information within the EU).

Art. 391. – This means that:

a) Reports of all serious adverse reactions arising from such studies within the EU should be reported on an expedited basis (i.e. within 15 days), to the Competent Authority of the Member State on whose territory the incident occurred, and in addition, for medicinal products authorised through the mutual recognition or decentralised procedures and for medicinal products which have been the subject of a referral procedure, to the Reference Member State. These reports should also be included in the PSURs (see Chapter VI);

b) Reports of all unexpected serious adverse reactions arising from such studies outside the EU should be reported on an expedited basis to the EMEA and to all Member States where the medicinal product is authorised. These reports should also be included in the PSURs (see Chapter VI);

c) Reports of non-serious adverse reactions, medicinal products within the EU as well as reports on expected serious occurring outside the EU should be compliant with the provisions of Chapter VI on PSURs;

Art. 392. – Marketing Authorisation Holders should ensure that they are notified by the investigator of serious adverse reactions and, if specified in the study protocol, of events (those not suspected by the investigator or the MAH to be adverse reactions).

Art. 393. – All adverse reactions/events including those which are considered non-serious, should be summarised in the final study report in frequency tables.

Art. 394. – (1) In certain study designs, such as case-control or retrospective cohort studies (see Data sources in Table VII.A), in which it is not feasible or appropriate to make an assessment of causality between medical events recorded and the medicinal products at individual case level, expedited reporting of Individual Case Safety Reports (ICSRs) is not mandatory.

(2) In case of doubt, the MAH should clarify the reporting requirements through the contact point referred to in Chapter VII section 4.1.1, according to the authorisation procedure of the medicinal product.

VII.4.3 Progress and Final Study Reports

VII.4.3.1 Studies requested by Competent Authorities

Art. 395. – (1) MAH should provide a study progress report anually, or more frequently as requested by the Competent Authorities (e.g. according to the Risk Management Plan milestones) or on their own initiative.

2) If the study is discontinued, a final report should also be submitted, which will include the reasons for stopping the study.

Art. 396. – (1) The content of the progress report should follow a logical sequence and should include all the available data which is judged relevant for the progress of the study; e.g. number of patients who have entered the study according to their status (exposure, outcome, etc.), problems encountered and deviations from the expected plan.

(2) After review of the report, Competent Authorities may request additional information.

Art. 397. – (1) A final study report should be submitted according to an agreed timetable (e.g. according to the stages of the Risk Management Plan considered important).

(2) For the content of the final report consideration should be given to the recommendations laid down in Table VII.C at the end of this Chapter.

(3) The findings of the study should be made public, preferably through scientific journals.

Art. 398. – (1) Both progress and final reports should be sent to the Competent Authorities of the Member States in which the study is being conducted and to the Competent Authority that requested the study.

(2) In case of medicinal products authorised through the mutual recognition or decentralised procedures, these reports should also be sent to the Reference Member State and, in case of centrally authorised medicinal products, to the EMEA, the Rapporteur and Co-Rapporteur.

(3) For evaluation of such reports, the same procedure as for evaluation of the protocol should be followed (see Chapter VII, Section 4.1).

Art. 399. – For post-authorisation safety studies that qualify as clinical trials, the criteria laid down in Minister of Public Health Order No. 904/2006 and related guidance (see Volume 10 of the Rules Governing Medicinal Products in the EU), should be followed, in addition to the requirements established in the present guidance.

VII.4.3.2 Studies performed at the MAH's initiative

Art. 400. – (1) Progress and final reports should be included or updated in the corresponding PSUR and/or Risk Management Plan.

(2) When a safety concern is raised, a report should be submitted immediately to the relevant Competent Authorities (including the Agency and (Co-) Rapporteur for centrally authorised products and the Reference Member State for medicinal products authorised through the mutual recognition or decentralised procedures).

(3) The findings of the study should be made public, preferably through scientific journals.

Art. 401. – For post-athorisation safety studies that qualify as clinical trials, the criteria laid down in Minister of Public Health Order No. 904/2006 and related guidance (see volume 10 of the Rules Governing Medicinal Products in the EU) should be followed, in addition to the requirements inlcluded in this Guideline from Volume 9a.

VII.5 Promotion of Medicinal Products

Art. 402. – (1) Post-authorisation studies should not be planned or conducted for the purposes of promoting the use of medicinal products.

(2) Company sales and marketing representatives should not be involved in studies in such a way that it could be seen as a promotional exercise, such as in the recruitment of patients and physicians.

VII.6 Participation of Healthcare Professionals

Art. 403. – Subject to the Healthcare Professional's terms of service, payment should be restricted to compensation of the Healthcare Professional for any additional time and expenses incurred.

Art. 404. – No additional payment or inducement for a Healthcare professional to participate in a post-authorisation safety study should be offered or given.

VII.7 Ethical Issues

Art. 405. – (1) Post-authorisation safety studies that qualify as clinical trials fall within the scope of Minister of Public Health Order No. 904/2006.

(2) For non-interventional post-authorisation safety studies, the Marketing Authorisation Holders and investigators should follow relevant national legislation in those Member States where this exists, in addition to the requirements given here.

Art. 406. – (1) The highest possible standards of professional conduct and confidentiality must always be maintained and legislation on data protection followed (see Directive 95/46/EC).

(2) The Patient's right to confidentiality is paramount.

(3) The Patient's identity should be replaced by a code in the study documents; only authorised persons should have access to identifiable personal details if the verification procedures demand inspection of such details.

(4) Responsibility for the retrieval of information from personal medical records lies with the Healthcare Professional(s) responsible for the Patient's care.

(5) Such information from personal medical records should be provided to the Marketing Authorisation Holder, who is thereafter responsible for the handling of such information.

Art. 407. – (1) It is recommended that non-interventional post-authorisation safety studies are referred to an Ethics Committee.

(2) Studies conducted entirely using records not containing any personal identifiers (e.g. anonymised records) may not require an ethical review of individual study protocols.

(3) National guidelines in this respect should be followed where they exist.

Art. 408. – According to European data protection legislation, explicit consent is required when the study plans to collect data containing personal identifiers, though some exceptions are envisaged.

VII.8 Procedure for Complaints

Art. 409. – A post-authorisation safety study, the objective, design or conduct of which gives cause for concern (e.g. using the study as a promotional activity), should be referred to the relevant Competent Authorities, and, if appropriate, to other bodies within Member States which are deemed to have the matter within their remit.

TABLE VII.A: EPIDEMIOLOGICAL METHODS FOR POST-AUTHORISATION SAFETY STUDIES

Spontaneous reporting schemes are valuable tools for providing safety signals in a continuous manner. In many situations, however, such passive surveillance should be complemented with more formal approaches in order to increase the sensitivity for risk identification or to confirm, characterise or quantify possible safety concerns.These more formal approaches are included under the term "post-authorisation safety studies".
1. Study Designs
Post-authorisation safety studies may adopt different designs depending on their objective. A brief description of the fundamental types of studies, as well as the types of data resources available, is provided hereafter. However, this table is not intended to be exhaustive and should be complemented with other widely available information sources (1-4). The ICH-E2E Guideline has been followed to a great extent in order to provide a harmonised view on this topic.
1.1 Metode de supraveghere activă Methods for Active Surveillance
Active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this medicinal product may be asked to complete a

brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

1.1.1 Sentinel Sites

Active surveillance may be achieved by reviewing medical records or interviewing patients and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Moreover, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weakness of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and haemodialysis centres. Institutional settings may have a greater frequency of use for certain medicinal products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may provide an efficient active surveillance system.

1.1.2 Intensive Monitoring Schemes

Intensive monitoring is a system of record collation in designated areas, e.g. hospital units or by specific Healthcare Professionals in community practice. In such cases, the data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be causally related to the medication. Monitoring may also be focused on certain major events that tend to be drug-related such as jaundice, renal failure, haematological disorders, bleeding. The major strength of such systems is that the monitors may document important information about the events and exposure to medicinal products. The major limitation is the need to maintain a trained monitoring team over time.

1.1.3 Prescription Event Monitoring

Prescription event monitoring is a method of active pharmacovigilance surveillance. In prescription event monitoring, patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire (5-6). Limitations of prescription event monitoring include incomplete physician response and limited scope to study products which are used exclusively in hospitals. More detailed information on adverse events from a large number of physicians and/or patients may

be collected.

1.1.4 Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry). Both types of registries, which only differ by the type of patient data of interest, may collect a battery of information using standardised questionnaires in a prospective manner. Disease/outcome registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations may help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition, or from outside the registry.

Exposure registries address populations exposed to medicinal products of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicinal product has a special impact on this group of patients.

Some exposure registries address exposures to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires.

Single cohort studies may measure incidence, but, without a comparison group, cannot provide proof of association. However, this study type may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan medicinal product indicated for a specific condition.

1.2 Comparative Observational Studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

1.2.1 Cross-sectional Studies (Survey)

These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for aetiologic research unless the exposures do not change over time. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for serial time-points can be captured. They may also be used to examine the crude association between exposure and outcome in ecologic analyses.

1.2.2 Cohort Study

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point of that follow-up.

Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the base of medication use and followed over time.

Cohort studies are useful when there is a need to know the incidence rates of adverse events in additional to the relative risks of adverse events. Multiple adverse events may also be investigated using the same data source in a cohort study.

However, it may be difficult to recruit sufficient numbers of patients who are exposed to a medicinal product of interest (such as an orphan medicinal product) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist. Cohort studies may be prospective or retrospective depending on when the outcome of interest occurs in relation to the commencement of the research: if the outcome occurs after the research begins, it would be prospective; if the outcome has already occurred when the investigation began, it would be retrospective.

1.2.3 Case-control Studies

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases.

Patients may be identified through an existent database or via the use of data particularly gathered for studies of interest. The controls should be selected in such a way that the prevalence to exposure to the medicinal product among the controls represents the prevalence of exposure in the source population.The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared using the odds ratio balance, which is an estimate of the relative risk of disease among those exposed, compared to those not exposed. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed exposure and medical outcome data in a relatively short period of time.

Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product(s) and one specific rare adverse event, as well as to identify risk factors for adverse events (or actually, effect-modifiers). Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the medicinal product exposure and the adverse event.

Under specific conditions, a case-control study may also provide the absolute incidence rate of the event. If all cases of interest (or a well-defined section of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated. As in cohort studies, case-control studies may be prospective or retrospective (see 1.2.2. of this Table).

When the source population within which the case-control study is conducted is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The term "nested case-control study" has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on those persons who make up the source population regardless of the duration of time they may have contributed to it (4).

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant aetiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

1.2.4 Other novel designs

Some novel designs have been described to assess the association between intermittent exposures and short-term events, including the case-series (7), the case-crossover (8) and the case-time-control (9) studies. In these designs only cases are used and the control information is obtained from past person-time experience of the cases themselves. One of the important strength of these designs is that those confounding variables that do not change between individuals are automatically matched.

1.3 Clinical trials

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions.

Furthermore, based on the pharmacological properties and the expected use of the medicinal product in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These

studies may include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.
Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children or patients with renal or hepatic disorders. Children, the elderly and patients with co-morbid conditions might metabolise medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.
In performing clinical trials, regulations of Directive 2001/20/EC, transposed through Minister of Public Health Order No. 904/2006 and related guidance (Volume 10 of the Rules Governing Medicinal Products in the EU31) should be followed.

1.3.1 Large simple trials

A Large Simple Trial is a specific form of clinical trial where large numbers of patients are randomised to treatment but data collection and monitoring is kept to the absolute minimum consistent with the aims of the study (10). This design is best used in pharmacovigilance to elucidate the risk-benefit profile of a medicinal product outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event. These studies qualify as clinical trials and are subject to Directive 2001/20/EC, transposed through the Minister of Public Health Order No. 904/2006 and related guidance (Volume 10 of the Rules Governing Medicinal Products in the EU32).

1.4 Other studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with exposures to medicinal products. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of medicinal products in specified populations.

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects as adverse events, such as the "background" incidence rate of or risk factors for the adverse event of interest, may be used to assist in putting spontaneous reports into perspective (1). For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

1.4.2 Drug Utilisation Study

Drug utilisation studies (DUS) describe how a medicinal product is marketed, prescribed and used in a population and how these factors influence outcomes, including clinical, social, and economic outcomes.
These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitent medication and other characteristics.
DUS may be used to determine if a medicinal product is being used in these populations.
From these studies, denominator data may be derived for use in determining rates of adverse reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS may be used to examine the relationship between recommended and actual clinical practice. These studies may help to determine whether a medicinal product has the potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies may include a lack of clinical outcome data or information of the indication for use of a medicinal product.

2. Data sources

Pharmacoepidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research.
There are two main types of automated databases, those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. They may not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data needed in certain researches, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmacoepidemiological studies or in their validation phase. Marketing Authorisation Holders should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results).
External validity should also be taken into account: as far as feasible the data source chosen to perform the study should include the population in which the safety

concerns have been raised. In case another population is involved, the Marketing Authorisation Holder should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored.
Regardless of the data source used, the privacy and confidentiality regulations that apply to personal data should be followed.

TABLE VII.B: ELEMENTS TO BE CONSIDERED IN THE PROTOCOL OF POST-AUTHORISATION SAFETY STUDIES AS APPROPRIATE
(Based on the Guidelines for good pharmacoepidemiology practices issued by the International Society for Pharmacoepidemiology.)

A	A descriptive title and version identifier (e.g. date)
B	The names, titles, degrees, addresses and affiliations of all responsible parties, including the principal investigator, co-investigators and a list of all collaborating primary institutions and other relevant study sites.
C	The name and address of the Marketing Authorisation Holder
D	An abstract of the protocol
E	The proposed study tasks, milestones and timelines
F	A statement of research objectives, specific aims and rationale *Research objectives describe the knowledge or information to be gained from the study. Specific aims list the measurements to be made and any hypotheses to be tested. The protocol should distinguish between a priori research hypotheses and hypotheses that are generated based on knowledge of the source data. The rationale explains how achievement of the specific aims will further the research objectives.*
G	A critical review of the literature to evaluate pertinent information and gaps in knowledge *The literature review should describe specific gaps in knowledge that the study is intended to fill. The literature review may encompass relevant animal and human experiments, clinical studies, vital statistics, and previous epidemiologic studies. The literature review should also cite the findings of similar studies and the expected contribution of the current study.*
H	A description of the research methods, including: 1. The overall research design, strategy and reasons for choosing the proposed design study. *Research designs include case-control, cohort, cross-sectional, nested case-control or hybrid designs.* 2. The population or sample to be studied *The population is defined in terms of persons, place, time period and selection criteria.*

	The rationale for the inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, details of sampling methods should be provided. 3. The strategies and data sources for determining exposures, health outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers, using validated measurements whenever possible *Data sources might include questionnaires, hospital discharge files, abstracts of primary clinical records, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews or exposure/disease registries.* 4. Clear operational definitions of health outcomes, exposures and other measured risk factors as well as selection criteria and comparison groups *An operational definition is one that can be implemented independently using the data available in the proposed study. For example, "PCP episode" does not represent an operational definition, whereas a better description would be "hospitalization with a primary discharge diagnosis of ICD-9-CM code 136.3".* 5. Projected study size, statistical precision and the basis for their determination *Describe the relation between the specific aims of the study and the projected study size in relation to each outcome.* 6. Methods used in assembling the study data *This should include a description of or reference to any pre-testing procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders or data entry personnel.* 7. Procedures for data management *Describe data management and statistical software programmes and hardware to be used in the study.* 8. Methods for data analysis *Data analysis includes all the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, to impute values or to modify raw data. Data analysis comprises comparisons and methods for analyzing and presenting results, categorizations as well as procedures to control sources of bias and their influence on results, e.g. possible impact of biases due to selection, misclassification, confounding and missing data. The statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or effect, for instance, should be presented. Any sensitivity analyses undertaken should also be described.* 9. A description of quality assurance and quality control procedures for all phases of the study *Mechanisms to ensure data quality and integrity should be described, including abstractions of original documents. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups.*

	10. Limitations of the study design, data sources and analytic methods *At a minimum, issues relating to confunding, misclassifications, selection, generalisability and random error should be considered. The likely success of efforts taken to reduce errors should be discussed.*
I	A description of plans for protecting human subjects *This section should include information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study.Conditions under which the study should be terminated (stopping rules) should be described; for prospective studies consider using a data safety monitoring board (DSMB) for this purpose.*
J	Management and reporting of adverse events/adverse reactions *This section should include the procedures for collecting, management and reporting of individual cases of adverse events or adverse reactions, as appropriate. If an exemption to the individual case reporting has been granted by the Competent Authorities, a mention should be made in this section along with a justification (the waiver must be attached as an annex).*
K	A description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of a *National Medicines Agency* *165* publication *There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g. results pertaining to the safety of a marketed medicinal product).*
L	Resources required to conduct the study *Describe time, personnel and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.*
M	Bibliographic references
N	Dated amendments to the protocol *Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, should be documented in writing.* *Any changes made after data analysis has begun should be documented as such and the rationale provided.*
O	Annexes *For any additional or complementary information on specific aspects not addressed in the body text (e.g. questionnaires, case report forms).*

TABLE VII.C: ELEMENTS TO BE CONSIDERED IN THE FINAL STUDY REPORT

(Based on the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology)

1	A descriptive title
2	An abstract
3	Purpose (objective) of the research, as stated in the protocol
4	The names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators
5	Name and address of the Marketing Authorisation Holder
6	Date son which the study was initiated and completed
7	Introduction with background, purpose and specific aims of the study
8	A description of the research methods, including: a) Source population and description of study subjects; b) Data collection methods and, if questionnaires or surveys are involved, complete copies (including skip patterns which were not answered); c) Transformations, calculations or operations on the data; d) Statistical methods used in data analysis.
9	A description of circumstances that may have affected the quality or integrity of the data. *Describe the limitations of study approach and the methods used to address them (e.g. response rates, missing or incomplete data).*
10	Data analysis *Include sufficient tables, graphs and illustrations to present the pertinent data and to reflect the analysis performed.*
11	Management and reporting of adverse events/adverse reactions
12	A statement of the conclusions drawn from the analysis of the data
13	A discussion of the implications of study results *Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research.*
14	References

CHAPTER VIII

Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action

VIII.1 Introduction

Art. 410. - Granting of a marketing authorisation for a medicinal product indicates that it is considered to have a satisfactory risk-benefit balance under the conditions defined in the Summary of Product Characteristics (SPC) and in accordance with the Risk Management Plan (where applicable) (see Chapter III), on the basis of the information available at that time.

Art. 411. – (1) During the post-authorisation period, larger and more diverse populations than those during the development phase of the medicinal product are likely to be exposed.

(2) New information on the benefits and risks of the medicinal product will be generated, and evaluation of this information and any safety concerns should be an on-going process, both by the Marketing Authorisation Holder and the NMA.

Art. 412. – Both the Marketing Authorisation holder and the NMA must keep abreast of all relevant information in order to fulfil the following responsibilities:

a) Ensuring that all sources of information are screened regularly to identify any potential signals;

b) Ensuring that appropriate action is taken in response to new evidence which impacts on the known risk-benefit balance;

c) Keeping the NMA, Healthcare Professionals (physicians) and Patients informed.

Art. 413. – This chapter has the following objectives:

a) outlines the responsibilities of Marketing Authorisation Holders in signal detection;

b) provides the principles on which an assessment of the risk-benefit balance should be based; and

c) outlines the steps that may be taken by Marketing Authorisation Holders in order to address a change in the risk-benefit balance.

VIII.2 Signal detection and evaluation

Art. 414. – (1) Signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may arise from any source including preclinical and clinical data (e.g. spontaneous reports from Healthcare Professionals or Consumers; epidemiological studies; clinical trials), published scientific and lay literature.

(2) Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases.

(3) Rarely, even a single report of an unexpected adverse reaction may contain sufficient information to raise a signal on or establish a casual association with the suspected medicinal product and impact on the risk-benefit balance.

Art. 415. – (1) The responsibilities of the MAH, and in particular of the QPPV, are provided in Chapter II section 2.

(2) It is the responsibility of the QPPV to provide the NMA with any information relevant to the evaluation of benefits and risks afforded by the medicinal product, including appropriate information on post-authorisation safety studies.

Art. 416. – The Marketing Authorisation Holder should immediately inform the NMA in all Member States where the medicinal product is authorised and additionally, for centrally authorised products, the EMEA of any prohibition or

restriction imposed by the Competent/regulatory authorities of any country in the world in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product.

Art. 417. – (1) The Marketing Authorisation Holder and the NMA should agree on the appropriate scope and timelines for evaluation, taking account of the authorisation procedure (see Chapter II.2.A and II.3 of Part II of Eudralex, volume 9a – Guideline for Competent Authorities and the EMEA) and agreed responsibilities for review.

(2) The MAH should provide a comprehensive evaluation of the issue and the risks in the context of the benefits at the earliest pportunity and no later than the agreed date specified in the written communications between the NMA and the MAH.

(3) This assessment should be sent to the NMA and also to the EMEA, in case of centrally authorised medicinal products.

VIII.3 Principles of Risk-Benefit Assessment

Art. 418. – (1) Overall risk-benefit assessment should take into account and balance all the benefits and risks referred to below.

(2) Risk-benefit assessment should be conducted separately in the context of each indication and population, which may impact on the conclusions and actions.

VIII.3.1 Assessment of benefits

Art. 419. – (1) When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data.

(2) The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use;

(3) The benefit is composed of several parameters including:

a) the extent to which the medicinal product cures or improves the disease/symptoms;

b) frequency of the answer;

c) duration of the answer;

d) quality of life.

(4) In the case of prophylactic medicinal products, the benefit may be considered as a reduction of the expected severity or incidence of the disease.

(5) With diagnostics, the benefit will be defined in terms of sensitivity and specificity or, in other words, false negative and false positive rates.

(6) Any available information on misuse of the medicinal 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.

(7) The quality and degree of evidence of risk should be taken into account; the benefit should, as much as possible, be expressed in quantitative terms, in a manner that makes it comparable to the risks.

VIII.3.2. Assessment of risks

Art. 420. – (1) Assessment of risk involves a stepwise process requiring identification, confirmation and characterisation (including identification of risk factors), and quantification of the risk in the exposed population.

(2) Overall assessment of risk should consider multiple sources of information, such as:

a) Spontaneous adverse reaction reports, national and international;

b) Adverse reaction data from studies which may or may not be company-sponsored;

c) In vitro and in vivo laboratory experiments;

d) Epidemiological data (see Table VII.A);

e) registries, for example of congenital anomaly/birth defects;

f) data published in the worldwide scientific literature or presented as abstracts, posters or communications;

g) Investigations on pharmaceutical quality;

h) Data on sales and medicinal product usage.

Art. 421. – (1) Important issues, which should be addressed in the assessment of adverse reactions, include evidence of causal association, seriousness, absolute and relative frequency and presence of risk factors, which may allow preventive measures.

(2) The quality and degree of evidence of risk should be taken into account.

(3) In the assessment of risks and consideration of regulatory action, it is important to note that rarely even a single case report may establish a causal association with the suspected medicinal product and impact on the risk-benefit balance.

4) Risk assessment should also take account of the potential for overdose, misuse, abuse, off-label use and medication errors.

Art. 422. – (1) When new safety concerns are identified, which, could have an impact on the overall risk-benefit balance of a medicinal product, the Marketing Authorisation Holder should propose appropriate studies to further investigate the nature and frequency of the adverse reactions.

(2) A new updated Risk Management Plan should be proposed accordingly (see Chapter III).

(3) The studies shoould comply with the guidance provided in Chapter I.7.

VIII.3.3 Risk-Benefit Assessment

Art. 423. – (1) Whenever possible, both benefits and risks should be considered in absolute terms and in comparison to alternative treatments.

(2) The magnitude of risk that may be considered acceptable is dependent on the seriousness of disease being treated and on the efficacy of the medicinal product; for example:

a) 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;

b) For medicinal products 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.

c) In situations where the main benefit is simple relief for minor illnesses in otherwise healthy individuals or where individuals are treated not only for their own but also for the benefit of the community (e.g. vaccination), risk levels must be extremely low.

d) In cases where therapeutic benefit is limited, even a few cases of a serious adverse reaction may suffice to render the risk-benefit balance as unfavourable.

e) if, for two medicinal products with essentially similar efficacy and types of adverse reactions, one or more serious adverse reactions were shown to differ in frequency, the risk-benefit balance of the medicinal product with the higher adverse reaction frequency may no longer be acceptable.

Art. 424. – The populations being treated must also be taken into account, as should off-label use.

VIII.4 Improvement of the risk-benefit balance

Art. 425. – (1) The MAH should aim to optimise the safe use and the risk-benefit balance of an individual medicinal product and ensure that the adverse effects of a medicinal product do not exceed the benefits within the population treated.

(2) The risk-benefit balance of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

Art. 426. – (1) The risk-benefit balance may be improved either by increasing the benefits (e.g. by restricting use to identified responders), or by reducing the risks by risk minimising measures (e.g. by contraindicating the use in patients particularly at risk, monitoring during treatment for early diagnosis of adverse reactions (see Table III.A for overview on risk minimisation methods).

(2) When proposing measures to improve the risk-benefit balance of a medicinal product, their feasability in normal conditions of use should be taken into account.

(3) If dose reaction is considered as a method of risk minimisation, the impact of dose reduction on efficacy shouuld be carefully evaluated.

Art. 427. - The following types of action may be necessary and may be initiated by the MAH or by the NMA:

a) variation of marketing authorisation(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the SPC and the package leaflet;

b) direct provision of important safety information to Healthcare Professionals and Patients (e.g. through letters and/or bulletins or via electronic media (see Chapter VIII, section 6).

Art. 428. – (1) If there are important new safety concerns requiring urgent action, the MAH should initiate an urgent safety restriction in accordance with Commission Regulations (EC) No. 1084/2003 and (EC) No. 1085/2003 followed by a type II variation.

(2) These measures should be immediately communicated to the NMA and in addition to the EMEA in case of a centrally authorised medicinal product.

(3) If no objections are raised within 24 hours after receipt of an application, the USR may be introduced and the corresponding application for the variation should be submitted without delay to the NMA and, with respect to centrally authorised medicinal products, the EMEA. See also Chapter II section 1, section 7 and Chapters II.2.A and II.3 of part II of the Eudralex, volume 9a – Guideline for Competent Authorisations and the EMEA).

VIII.5. Withdrawal of a medicinal product from the market on risk-benefit grounds

Art. 429. – (1) In the event that the overall risk-benefit balance is considered to be unfavourable and proposed risk minimisation measures are considered inadequate to redress the balance, the medicinal product should be withdrawn from the market and Healthcare Professionals and Patients/the public should be informed as appropriate (see Chapter VIII, section 6).

(2) Such action may be taken voluntarily by the MAH.

(3) It is recommended that any such intended measure be discussed at an early stage with all Competent Authorities concerned.

(4) All concerned Competent Authorities should be informed immediately of any definite action.

Art. 430. – For reporting requirements for Individual Case Safety Reports following withdrawal of a marketing authorisation see Chapter V.

VIII.6. Communication

Art. 431. – (1) In the event of a medicinal product withdrawal, an urgent safety restriction or an important variation, the content of Public Statements, Direct Healthcare Professional Communication (DHPC), Healthcare Professionals, Patients and the general public, including the time frame for the distribution of such communication, should be agreed with the relevant Competent Authorities.

(2) According to Art. 816 (8) of law 95/2006, the MAH should not communicate to the public pharmacovigilance-related information without informing the NMA.

ANNEX 1

Definitions

Abuse(s) of medicinal products = Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects (Article 1(16) of Directive 2001/83/EC).

Consumer = a person who is not a Healthcare Professional, such as a patient, lawyer, friend or relative, parent, children of a patient.

Data lock point = the term designated as the cut-off date for data to be included in a periodic safety update report.

International Birth Date (IBD) (of a medicinal product) = 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. For a medicinal product for which the international birth date is not known, the MAH can designate an International Birth Date (IBD) to allow synchronisation of submission of PSURs.

EU Birth Date (of a medicinal product) = 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 centralized procedure, the EU Birth Date is the date of the marketing authorisation granted by the European Commission (EC) (the date of the Commission Decision).
- For medicinal products authorised through mutual recognition/decentralized procedure, the EU Birth Date is the date of the marketing authorisation granted by the Reference Member State (RMS).
- For medicinal products authorised through purely national procedure, the MAH may propose a birth date which can be applied to reporting requirements across all EU Member States.

Company Core Data Sheet (CCDS) = A document prepared by the Marketing Authorisation Holder containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the medicinal product.

Company Core Safety Information (CCSI) = All relevant safety information contained in the company core data sheet prepared by the Marketing Authorisation Holder and which the Marketing Authorisation Holder requires to be listed in all countries where the company markets the medicinal product, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed/unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected/unexpected are determined for expedited reporting.

Adverse event (or adverse experience) (AE) = any untoward occurence in a patient or clinical-trial subject, administered a medicinal product and does not necessarily

have to have a causal relationship with this treatment [article 2 (m) of Directive 2001/20/EC]. An Adverse Event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Healthcare Professional = For the purposes of reporting suspected adverse reactions, Healthcare Professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners.

Invented Name = the name of a medicinal product, as it appears in the product information or the common or scientific name together with the trademark or the name of the MAH followed by the strength and the pharmaceutical form of the medicinal product. The common name is the international common name recommended by WHO or, if it doesn't exist, the usual common name.

Medicinal product = a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (Art. 695(2) of law 95/2006).

Risk-benefit balance = An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety, or efficacy of the medicinal product as regards Patient's health or public health) (Article 695(29) of Law 95/2006).

Periodic Safety Update Report (PSUR) = the periodical reports containing the records referred to in Article 816 of Law 95/2006 and in Article 24(3) of Regulation (EC) No. 726/2004.

Adverse reaction/adverse drug reaction (ADR)/suspected adverse (drug) reaction = a reposnse to a noxious and unintended medicinal product 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 (Article 695(10) of Law No. 95/2006). Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (in accordance with the ICH-E2A guideline – which means that a causal relationship cannot be excluded). Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the SPC or other conditions laid down for the marketing and use of the medicinal product (including prescribed doses higher than those recommended, overdoses or abuse).

Individual Case Safety Report = a document providing the most complete information related to an individual case at a certain point of time.

An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products, to an individual Patient at a particular point of time.

Serious adverse reaction = Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the Patient or might requireintervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscarsias or convulsions that do not result in hospitalization or development of dependency or abuse.

Unexpected adverse reaction = Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

This includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product. For products authorized nationally, the relevant SPC is that approved by the Competent Authority in the Member State to whom the reaction is being reported. For centrally authorized products, the relevant SPC is the SPC authorized by the European Commission. During the time period between a CHMP opinion in favour of granting a marketing authorization and the Commission Decision granting the marketing authorization, the relevant SPC is the SPC annexed to the CHMP Opinion.

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

Unlisted adverse reaction = An adverse reaction that 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 medicinal product.

Spontaneous report/notification

An unsolicited communication by a Healthcare Professional or Consumer to a company, regulatory authority or other organization (e.g. WHO, a regional centre, a poison control centre) which fulfills the following three conditions:

- it describes one or more suspected adverse reactions in a patient
- the patient was given one or more medicinal products
- it does not derive from a study or any organized data collection scheme.

Healthcare Professionals or consumers may be stimulated to report a suspected adverse reaction by several situations including:

- A Direct Healthcare Professional Communication
- Early Post-Marketing Phase Vigilance (EPPV), e.g. in Japan
- A report in the press
- Direct questioning of Healthcare Professionals by company representatives.

In these circumstances, provided the report meets the three conditions above, it should be considered a spontaneous report.

Risks relating to the use of a medicinal product = any risk concerning the safety, quality or efficacy of a medicinal product relating to the Patient's health or public health and any risk or unwanted effects on the environment [Art. 695 (28) of Law No. 95].

Risk Management System = a risk management system shall comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions (Art. 34 of Regulation (EC) No. 1901/2006).

Clinical Trial = any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in one site or multiple sites, whether in one or more Member States. An investigational medicinal product is the pharmaceutical form of an active/placebo substance which is tested or used as a reference in a clinical trial, including already authorised medicinal products, but which are used, exposed or packaged otherwise than their authorised form or which are used for an unauthorised indication or in view of obtaining more detailed information on the authorised form.

Non-interventional trial = a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data (Article 21 of the Minister of Public Health Order No. 904/2006).

Post-autorisation study = Any study conducted within the conditions laid down in the SPC and other conditions laid down for the marketing of the product or under normal conditions of use. A post-authorisation study falls either within the definitions of a clinical trial or a non-interventional study and may also fall within the definition of a post-authorisation safety study.

Solicited sources of Individual Case Safety Reports = organised data collection schemes, which include clinical trials, registries, named-patient use programmes, other patient support and disease management programmes, surveillance of patients, healthcare providers or information gathering on efficacy or patient compliance.

For the purpose of safety reporting, solicited reports should be classified as Individual Case Reports from studies and therefore should have an appropriate causality assessment by a healthcare professional or a MAH.

ANNEX 2

Terms in relation to risk management

Additional risk minimisation activity = A risk minimisation activity put in place to reduce the probability of an adverse reaction occurring its severity should it occur which is not a routine risk minimization activity – e.g. additional educational material or use of one of the other risk minimization activities in Table III.A.

Identified Risk = An untoward occurrence for which there is adequate evidence of an association, with the medicinal product of interest; examples of identified risks include:

- An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data
- An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest suggests a causal relationship
- An adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausability, such as anaphylactic reactions or application site reactions.

Important identified risk, important potential risk or important missing = an identified risk, potential risk or potential information that could impact on the risk-benefit balance of the medicinal product or have implications for public health.

Missing information = information about the safety of a medicinal product which is not available at the time of submisson of the EU Risk Management Plan (EU-RMP) and which represents a limitation of the safety data with respect to predicting the safety of the medicinal product in the marketplace.

Potential Risk = An untoward occurence, for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed; examples of potential risks include:

- non-clinical safety concerns that have not been observed or resolved in clinical studies
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship

- a signal arising from a spontaneous adverse reaction reporting system
- an event which is known to be associated with other medicinal products of the same class or which could be expected to occur based on the properties of the medicinal product.

Risk Management System (RMS) = a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions (Article 34 of Regulation (EC) No. 1901/2006 concerning medicinal products for human use.

Risk Minimisation (RM) = set of activities used to reduce the probability of an adverse reaction occuring or its severity should it occur.

Routine Pharmacovigilance = Pharmacovigilance activities as specified in Regulation 726/2004/EC and Law No. 95/2006, Title XVII – The medicinal product that should be conducted for all medicinal products which must be undertaken for all medicinal products..

Routine risk minimisation activities = the warnings and information contained within the SPC and Patient Leaflet, and the careful use of labelling and packaging, which aim to reduce the probability of an adverse reaction occurring or its severity should it occur.

Safety Concern = an important identified risk, important potential risk or important missing information.

Target Population = The Patients who might be treated by a medicinal product in accordance with the indication(s) and contraindication(s) in the SPC.

ANNEX 3

Template for cover for PSUR condition

(serial number) **PERIODIC SAFETY UPDATE REPORT**
for
Active substance: (name)
ATC code:
Medicinal products covered:

Name of product	MA Number	Date of marketing authorisation (underlined EU birth	MAH

		date)	

Authorisation procedure in the EU: (Centralised/Mutual recognition/National)
International birth date: (Date)

Period covered by this report: from date to date **Date of this report:** (Date)

Volume: Number/total number of volumes

Other information:
Data lock point of the next PSUR:
(Date)
Name and address of the MAH:
(Name)
(Address)

Name and contact details of the QPPV:
Name
Address
Telephone number
Fax number
E-mail address
Signature: (signature)

List of serial numbers

Serial number	Period covered

Distribution list[x]

Competent Authority in the EU	Number of copies

[x] For medicinal products authorised through the mutual recognition or decentralised procedure the Reference Member State and the Concerned Member States should be indicated.

A
N
N
E
X

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Template for PSUR section "Worldwide Marketing Authorisation Status"

Country	Date of authorisation	Launch date	Invented name	Comme

ANNEX 5

Example of listing

MAH No.	Country	Source	Age/ sex	Daily Dose mg/day	Date of onset of adverse reaction/ time to onset	Dates of treatment/ treatment duration	Reaction Description	Outcome	C

ANNEX 6

Example of Summary Tabulation
Number of Reports by Term (signs, symptoms, diagnoses) from spontaneous (medically confirmed), clinical trials and literature cases: All serious reactions
An * indicates an unlisted reaction

Body system/adverse	Spontaneous/Regulatory	Clinical trials	Literature

reaction term	Bodies		
CNS			
Hallucinations*	2		0
0			
etc.	-		-
-			
etc.			

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

Sub-total			
Etc.			
Total			

In another footnote, the number of patient-cases that represent the tabulated terms should be given (ex. x-spontaneous/regulatory, y-clinical trials and z-literature cases).