RISK MANAGEMENT TRENDS

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Risk Management Plan and Pharmacovigilance System - Biopharmaceuticals: Biosimilars

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1. Introduction

The chapter addresses similar biological medicinal products (biosimilars) safety monitoring and describes the activities that should be developed in their risk minimisation plan. This is an issue that has aroused great interest with the recent expiration of biotech drugs patents and the advent of biosimilar products on the market.

2. Risk management

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. However, not all actual or potential risks will have been identified when an initial authorisation is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole.

The management of a single risk can be considered as having four steps, *risk detection*, *risk assessment, risk minimisation and risk communication* which are summarized at table 1. 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. 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. Meanwhile Table 1 explains the management of a single risk, Figure 1 goes further and describes a complete risk management system, the so-called "Risk Management Plan" (EU-RMP) which contains two parts: *pharmacovigilance* and *risk minimization*. It covers how the safety of a product will be monitored and measured to reduce risk.

This chapter focuses on the activities that should be developed in the risk minimisation plan to be applied to biopharmaceuticals and more specifically to biosimilars (medicines similar but not identical to a biological medicine approved once patent lifetime for the original biotherapeutic has expired). Biopharmaceuticals often exhibit safety issues such as immunotoxicity that may lead to a loss of efficacy and/or to side effects (Giezen et al., 2009;

Stanulovic et al., 2011). The CHMP guidelines on biosimilars states that data from pre-authorisation clinical studies normally are insufficient to identify all potential differences with the reference product (Giezen et al., 2008). The main regulatory basis related to risk management are listed on Table 2.

DIFFERENT STEPS OF RISK MANAGEMENT		
RISK DETECTION AND ASSESSMENT	*Identify the risks*	Preclinical studies
		Harms identified in clinical trials & meta-analyses
		Formal mortality and morbidity studies
	Understand the risk	Rigorous case definition
		Case series analysis
		Clear description in label
	Monitor the risk	Post marketing surveillance
		Database analyses
		Prospective cohort studies and registries (to study potentially rare but important risks where risk identification or product attribution is difficult)
RISK MINIMISATION AND COMMUNICATION	*Communicate the risk*	Advice in label (not enough to communicate specific risk minimisation activities or change behaviours)
		Partnership with regulators
		Education of physicians, patients, company staff
	Act to reduce the risk	Limited distribution
		Limited prescribing rights
		Contra-indicate for certain groups, indications, routes of administration
		Advice for high risk groups
	Measure outcome of interventions	

Table 1. Risk Management steps

REGULATORY FOCUS ON RISK MANAGEMENT	
ICH E2E	Pharmacovigilance Planning (Nov 2004)
EMA	The Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005). The Guideline has been included as chapter I.3 of Volume 9A. Annex C: Template for EU Risk Management Plan (EMEA/192632/2006)
GMP	ANNEX 20 Quality Risk Management (Feb 2008)

Table 2. Risk Management Legal Framework

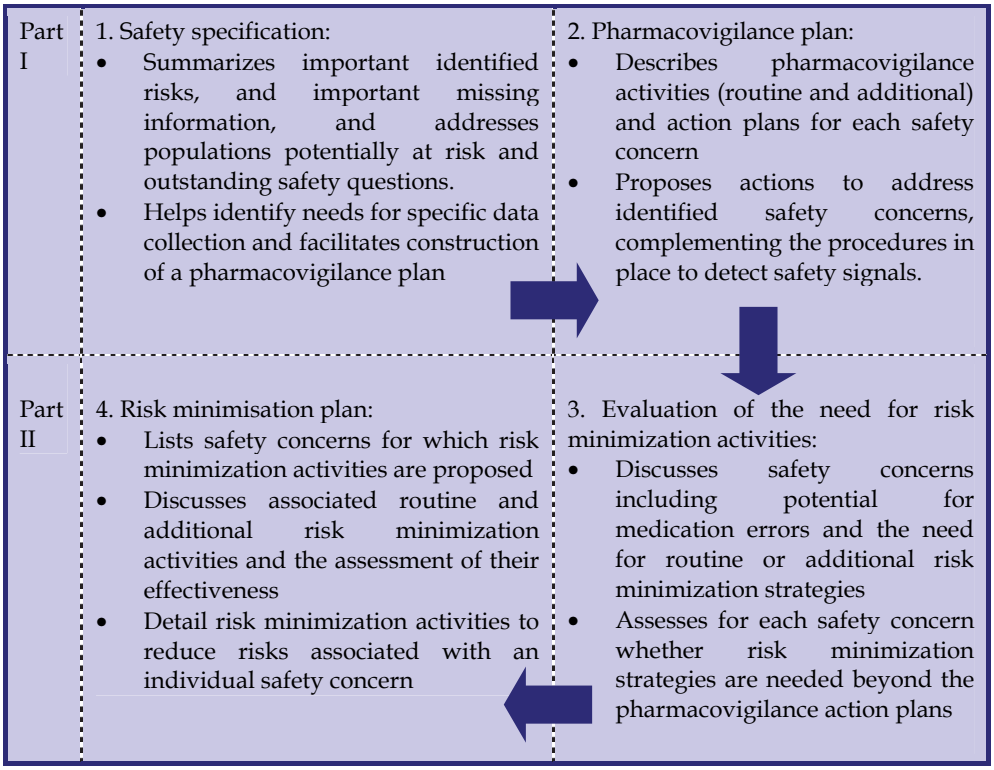

Fig. 1. Risk Management Plan development

2.1 Risk identification and safety specification

This is a summary of the important specified risks of a medicinal product, important potential risks, and important missing information. It also addresses the populations potentially at risk and outstanding safety questions, which warrant further investigation to refine understanding of the benefit-risk profile during the post-authorisation period. Table 3 explains the different considerations to take in mind when collecting safety data during the non-clinical and clinical development of a biosimilar medicinal drugs.

The safety issues identified in the safety specification should be based on the information related to the safety of the product included in the Common Technical Document (CTD), especially the overview of safety, benefits and risks conclusions and the summary of clinical safety (Zúñiga & Calvo, 2010a). The safety specification can be a stand-alone document, usually in conjunction with the pharmacovigilance plan, but elements can also be incorporated into the CTD.

Clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued risk-benefit assessment.

Even if the efficacy is shown to be comparable, the biosimilar product can exhibit a different safety profile in terms of nature, seriousness, or incidence of adverse reactions. Marketing Authorisation Holder (MAH) should provide safety data prior to marketing authorisation,

but also post-marketing as possible differences might become evident later, even though comparability with regard to efficacy has been shown. It is important to compare adverse reactions in terms of type, severity and frequency between biosimilar and reference medicinal product. Attention should be paid to immunogenicity and potential rare serious adverse events, focusing on patients with chronic treatments. The risk management plans for biosimilars should focus on:

- Heightened pharmacovigilance measures
- Conduct antibody testing
- Implement special post-marketing surveillance

For the marketing authorisation application a risk management program / pharmacovigilance plan is required. This includes a risk specification describing the possible safety issues caused by the differences (i.e. hostcells, manufacturing, purification, excipients etc.) of the biosimilar to the reference product.

ELEMENTS OF THE SAFETY SPECIFICATION	
Non-Clinical	
Non-clinical safety findings that have not been adequately addressed by clinical data	• Toxicity • General pharmacology • Drug interactions • Other toxicity-related information and data
	If the product is intended for use in special populations, consideration should be given to wether specific non-clinical data needs exist.
Clinical	
Limitations of the human safety database	• Discussion of the implications of the database limitations with respect to predicting the safety of the product in the marketplace • Reference to the populations likely to be exposed during the intended or expected use of the product in medical practice. • Discussion of the world-wide experience: - The extent of the world-wide exposure - Any new or different safety issues identified - Any regulatory actions related to safety • Detail the size of the study population using both numbers of patients and patient time exposed to the drug. This should be stratified by relevant population categories. • Detail the frequencies of adverse drug reactions detectable given the size of the database. • Detail suspected long-term adverse reactions when it is unlikely that exposure data is of sufficient duration and latency.
Populations not studied in the pre-authorisation phase	• Discussion of which populations have not been studied or have only been studied to a limited degree in the pre-authorisation phase and the implications of this with respect to predicting the

	safety of the product in the marketplace: - Children - The elderly - Pregnant or lactating women - Patients with relevant co-morbidity such as hepatic or renal disorders - Patients with disease severity different from that studied in clinical trials - Sub-populations carrying known and relevant genetic polymorphism - Patients of different racial and/or ethnic origins • Reference the relevance of inclusion and exclusion criteria in relation to the target population
Adverse events/ adverse reactions	The risk data should be presented according to the specific format described in section 3.6.2.c) of the Volume 9A The rules governing medicinal products in the EU (March 2007)
	• List the important identified and potential risks that require further characterization or evaluation (*identified* or *potential* risks)
	Identified Risks (an untoward occurrence for which there is adequate evidence of an association with the medicinal products of interest). • Include more detailed information on the most important identified adverse events/ adverse reactions (serios, frequent and/or with an impact on the balance of benefits and risks of the medicinal product). • Include evidence bearing on a casual relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. • Discussion of risk factors and potential mechanisms
	Potential risks (an untoward occurrence 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). • Description of important potential risks with the evidence that led to the conclusion that there was a such a type of risk
Identified and potential interactions including food-drug and drug-drug interactions	• Discussion of identified and potential pharmacokinetic and pharmacodynamic interactions • Summary of the evidence supporting the interaction and the possible mechanism • Discussion of the potential health risks posed for the different indications and in the different populations • Statement listing the interactions that require further investigation

Epidemiology	• Discussion of the epidemiology of the indications including incidence, prevalence, mortality and relevant co-morbidity (take into account stratification by age, sex and racial/ethnic origin) • Discussion of the epidemiology in the different regions with emphasis on Europe • Review the incidence rate of the important adverse events that require further investigation among patients in whom the medicinal product is indicated • Include information on risks factors for an adverse events
Pharmacological class effects	• Identify risks believed to be common to the pharmacological class (justified those risks common to the pharmacological class but not thought to be a safety concern)
Additional EU requirements	• Discussion of the following topics: - Potential for overdose - Potential for transmission of infectious agents - Potential for misuse for illegal purposes - Potential for off-label use - Potential for off-label paediatric use
Summary	
• Important identified risks • Important potential risks • Important missing information	

Table 3. Elements of the risk identification and safety specification (EMA, 2006)

2.2 Pharmacovigilance plan

The pharmacovigilance plan should be based on the safety specification and propose actions to address the safety concerns identified (relevant identified risks, potential risks and missing information). An action plan model can be found on Table 4. 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.

Safety concern	**Planned action (s)**
Important identified risks	<> List
Important potential risks	<> List
Important missing information	<> List

Table 4. Summary of safety concern and planned pharmacovigilance actions (EMA, 2006)

The plan can be discussed with regulators during product development, prior to approval of the new product or when safety concerns arise during the post-marketing period. It can be a stand-alone document but elements could also be incorporated into the CTD (table 5) (Zúñiga & Calvo, 2010b).

ROUTINE PHARMACOVIGILANCE	ADDITTIONAL PHARMACOVIGILANCE ACTIVITIES
• For medicinal products where no special concerns have arisen	• For medicinal products with important identified risks, important potential risks or important missing information • The activities will be different depending on the safety concern to be addressed

Table 5. Pharmacovigilance activities

The ***action plan*** for each safety concern should be presented and justified according to the following structure:

- Safety concern
- Objective of proposed actions
- Actions proposed
- Rationale for proposed actions
- Monitoring by the MAH for safety concern and proposed actions
- Milestones for evaluation and reporting

Protocols for any formal studies should be provided. Details of the monitoring for the safety concern in the clinical trial will include stopping rules, information on the drug safety monitoring board and when interim analyses will be carried out.

The outcome of the proposed actions will be the basis for the decision making process that needs to be explained in the EU-RMP.

CHMP biosimilars guidelines emphasise need for particular attention to pharmacovigilance, especially to detect rare but serious side effects.

Important issues include:

- Pharmacovigilance systems should differenciate between originator and biosimilar products (so that effects of biosimilars are not lost in background of reports on reference products).
- Ensure Traceability (importance of the international nonproprietary name, INN).

2.3 Evaluation of the need for risk minimisation activities

For each safety concern, the Applicant/Marketing Authorisation Holder should assess whether any risk minimisation activities are needed. 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. It is possible that the risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by the careful use of labelling and packaging, i.e. routine risk minimisation activities. If an Applicant/Marketing Authorisation Holder is of the opinion that no additional risk minimisation activities beyond these are warranted, this should be discussed and, where appropriate, supporting evidence provided.

However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary. If these are required, they should be described in the risk minimisation plan which should be included in Part II of the EU-RMP.

Within the evaluation of the need for risk minimisation activities, the Applicant/Marketing Authorisation Holder should also address the potential for medication errors (some examples are listed on Table 6) and state how this has been reduced in the final design of the pharmaceutical form, product information, packaging and, where appropriate, device.

POTENTIAL REASONS FOR MEDICATION ERRORS	
Naming	Taking into account the Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed through the Centralised Procedure. CPMP/328/98 Rev 5, Dec 2007.
Presentation	Size, shape and colouring of the pharmaceutical form and packaging
Instructions for use	Regarding reconstitution, parenteral routes of administration, dose calculation
Labelling	

Table 6. Potential reasons for medication errors that the applicant needs to take into account

Applicants/Marketing Authorisation Holders should always consider the need for risk minimisation activities whenever the Safety Specification is updated in the light of new safety information on the medicinal product.

2.4 The risk minimization plan

The risk minimisation plan details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern. When a risk minimisation plan is provided within an EU-RMP, the risk minimisation plan should include both routine and additional risk minimisation activities. A safety concern may have more than one risk minimisation activity attached to an objective.

The risk minimisation plan should list the safety concerns for which risk minimisation activities are proposed. The risk minimisation activities, i.e. both routine and additional, related to that safety concern should be discussed. 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. Table 7 shows how to approach the risk minimisation plan.

3. Postmarketing pharmacovigilance

MAHs should ensure that all information relevant to a medicinal product´s balance of benefits and risks is fully and promptly reported to the Competent Authorities; for centrally authorised products, data also should be reported to EMA. The MAH must have a qualified person responsible for pharmacovigilance available permanently and continuously.

3.1 Legal framework

The legal framework for pharmacovigilance of medicinal products for human use in the European Union (EU) is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC

(Title IX) on the Community code relating to medicinal products for human use, as last amended by Directive 2004/24/EC and by Directive 2004/27/EC (EudraLex, 2007).

Safety concern	
Routine risk minimisation activities (i.e. product information, labelling and packaging)	<*short description of what will be put in the Summary of Product Characteristics (SPC), labelling etc to minimize risk e.g. warning in 4.4 (special warnings and precautions for use), that caution should be used in patients with cardiac failure, etc*>
Additional risk minimisation activity 1 (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes)	*Objective and rationale*
	Proposed actions
	Criteria to be used to verify the success of proposed risk minimisation activity
	Proposed review period
Additional risk minimisation activity 2, etc	*Objective and rationale*
	Proposed actions
	Criteria to be used to verify the success of proposed risk minimisation activity
	Proposed review period

Table 7. Information required for each important identified or potential risk for which additional risk minimisation measures are planned

For the biosimilar medicinal drugs approved in the Community through the centralised procedure, legal provisions are set forth in *Regulation (EC) No. 726/2004* (Title II, Chapter 3) (European Commission, 2004) and Commission *Regulation (EC) No. 540/95* (reporting of nonserious unexpected adverse reactions). The legal texts are supported by a series of guidelines, some of which have been compiled into Eudralex (Volume 9-Pharmacovigilance) (EudraLex, 2004). The requirements explained in these guidelines are based on the International Conference on Harmonisation (ICH) guidelines but may be further specified or contain additional request in line with Community legislation.
The obligations concerned with the monitoring of adverse reactions occurring in clinical trials do not fall within the scope of pharmacovigilance activities. The legal framework for such obligations is Directive 2001/20/EC. However, Part III of Volume 9A deals with

technical aspects relating to adverse reaction/event reporting for pre- and post-authorisation phases.
Pharmacovigilance activities are within the scope of quality, safety and efficacy criteria, because new information is accumulated on the normal use of medicinal products in the EU marketplace. Pharmacovigilance obligations apply to all authorised medicinal products, including those authorised before 1 January 1995 (Fruijtier, 2006), whatever procedure was used for their authorisation.
At approval there is limited clinical experience. Accurate pharmacovigilance and correct attribution of adverse events is vital.
Pharmacovigilance has been defined by the Worl Health Organization as the science and activities relating to the detection, assessment, unsderstanding and prevention of adverse effects or any other medicine-related problem (EudraLex, 2007).
The three main goals in Pharmacovigilance are:

- Protect the patients
- Protect the Pharmaceutical Company
- Comply with regulatory Requirements

3.2 Pharmacovigilance for centrally authorised productsreporting of adverse reactions and other safety-related information

Pre-Authorisation Phase

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

Post-Authorisation Phase

Suspected adverse reactions related to centrally authorised products are reported directly by Healthcare Professionals, to each Member State. Marketing Authorisation Holders report serious suspected adverse reactions to the Member State in which the reactions occurred, within 15 calendar days of receipt. Each Member State is responsible for following up the Individual Case Safety Reports it receives to obtain further information as necessary.
The Member States should forward to the Agency serious suspected adverse reactions occurring within their territories.
The Agency and all Member States should receive directly from the Marketing Authorisation Holders suspected serious and unexpected adverse reactions that occur in a country outside of the EU.

The Agency should ensure that all relevant information about suspected serious unexpected adverse reactions from outside the EU are entered into the EudraVigilance database, and Member States should ensure that data on suspected serious adverse reactions occurring in their territory are uploaded into the EudraVigilance database.
Table 8 shows the main aspects to be considered relating biosimilar drugs safety during pre-autorisation and post-authorisation phase. The table highlights the additional reporting requirements for biosimilars when comparing to general safety reporting.

REPORTING OF ADVERSE REACTIONS AND OTHER SAFETY-RELATED INFORMATION		
	GENERAL REPORTING (Scharinger, 2007)	BIOSIMILARS REPORTING
PRE-AUTHORISATION PHASE	• All Suspected Unexpected Serious Adverse Reactions (SUSARs) • Sponsors to report to: - Concerned Member States (paper or electronically) - Concerned Ethics Committees (on paper) - EudraVigilance Trial Module (EVCTM) at the EMA (electronically) • Legal basis: Volume 10 of EudraLex- Clinical Trials guidelines	• Clinical safety data always required, even if efficacy is shown to be comparable • Sufficient number of patients to compare common Adverse Drug Reactions (ADRs) between referenced and claimed biosimilar products (type, severity, frequency) • Risk specification and pharmacovigilance plan part of the application dossier, as per EU legislation and guidelines • Pharmacovigilance systems/ procedures should be in place (traceability as per current EU guidelines)
POST-AUTHORISATION PHASE	• Adverse Drug Reactions/ Individual Case safety Reports (ICSRs) • Electronic reporting: - Mandatory e-reporting of ICSRs - Definition of exceptional circumstances that prevent electronic reporting (mechanical, program, electronic or communication failure) - Fall-back procedures to maintain expedited reporting compliance are established • Periodic Safety Update Reports (PSURs) from MAH to the Competent Authorities • Legal basis: Volume 9A of EudraLex- Pharmacovigilance	• Benefit-risk assessment on an ongoing basis. Importance of clinical experience with biologics: 2-3 years after market approval to adequately validate risk/benefit profile. • Risk management programme may be required if rare but serious adverse reactions.

Table 8. Biosimilars: pre and post-authorisation safety concerns

3.3 Monitoring of the safety profile

Signal Identification

It is likely that many potential signals will emerge in the early stages of marketing and it will be important for these to be effectively evaluated.
A signal of possible unexpected hazards or changes in severity, characteristics or frequency of expected adverse effects may be identified by:

- the Marketing Authorisation Holders;
- the Rapporteur;
- the Member States;
- the Agency in agreement with the Rapporteur

It is the responsibility of each Member State to identify signals from information arising in their territory. However, it will be important for the Rapporteur and the Agency to have the totality of information on serious adverse reactions occurring inside and outside the EU in order to have an overall view of the experience gathered with the concerned centrally authorised product.
As a matter of routine, the Rapporteur should continually evaluate the adverse reactions included in the EudraVigilance system and all other information relevant to risk-benefit balance in the context of information already available on the product, to determine the emerging adverse reactions profile. Additional information should be requested from the Marketing Authorisation Holder and Member States as necessary, in liaison with the Agency.
When a Member State other than the Rapporteur wishes to request information from the Marketing Authorisation Holder (apart from routine follow-up of cases occurring on their own territory) for the purposes of signal identification, the request should be made in agreement with the Rapporteur and the Agency.
Member States will inform the Rapporteur(s) and the Agency when performing class-reviews of safety issues which include centrally authorised products.
The Pharmacovigilance Working Party (PhVWP) should regularly review emerging safety issues which will be tracked through the *Drug Monitor* system.

Signal Evaluation

As signals of possible unexpected adverse reactions or changes in the severity, characteristics or frequency of expected adverse reactions may emerge from many different sources of data (see above), the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal.
Irrespective of who identified the signal, a signal evaluation should be carried out by:

- the Rapporteur; or
- the Member State where a signal originated.

The Rapporteur should work closely with the identifier of the signal to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the Assessment Report on the risk-benefit balance, by the Rapporteur or the Member State where the signal originated from, or jointly.
A Member State other than that of the Rapporteur should not start a full evaluation prior to having contacted the Agency and the Rapporteur, in order to prevent any unnecessary duplication of effort.
At request of the CHMP, the PhVWP evaluates signals arising from any source and keeps any potential safety issues under close monitoring.

Evaluation of Periodic Safety Update Reports

The Marketing Authorisation Holder is required to provide Periodic Safety Update Reports (PSURs) to all the Member States and the Agency. It is the responsibility of the Agency to ensure that the Marketing Authorisation Holder meets the deadlines.
The Marketing Authorisation Holder should submit any consequential variations simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CHMP.
It is the responsibility of the Rapporteur to evaluate and provide a report in accordance with the agreed timetable and to determine what issues if any need to be referred to the PhVWP and CHMP.
Actions required following the evaluation of a PSUR will be determined by the Rapporteur and the Marketing Authorisation Holder will be informed by the Agency, after agreement by the CHMP.
Where changes to the marketing authorisation are required, the CHMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision (Ebbers et al., 2010).

Evaluation of Post-Authorisation Studies, Worldwide Literature and Other Information

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

Evaluation of Post-Authorisation Commitments

It is the responsibility of the Agency to ensure that the Marketing Authorisation Holder meets the deadlines for the fulfilment of specific obligations and follow-up measures, and that the information provided is available to the Rapporteur and the CHMP.
The Marketing Authorisation Holder should submit any consequential variations simultaneously with the requested information for the fulfilment of specific obligations/follow-up measures, in order to prevent any unnecessary duplication of effort. Variations may, however, also be requested subsequently by the Rapporteur, after agreement by the CHMP.
For marketing authorisations granted under exceptional circumstances, specific obligations will be set out in Annex II.C of the CHMP Opinion. Specific obligations should be reviewed by

the Rapporteur, at the interval indicated in the Marketing Authorisation and at the longest annually, and should be subsequently agreed by the CHMP. As above, the Rapporteur should determine what issues if any need to be referred to the PhVWP and CHMP.
For marketing authorisations granted under exceptional circumstances, the annual review will include a re-assessment of the risk-benefit balance. The annual review will in all cases lead to the adoption of an Opinion which will be forwarded to the European Commission for preparation of a Decision.
For all marketing authorisations (whether or not the authorisation is granted under exceptional circumstances) follow-up measures may be established, which are annexed to the CHMP Assessment Report. These will be reviewed by the Rapporteur, and will be considered by PhVWP and CHMP at the Rapporteur's request.
Where changes to the marketing authorisation are required, the CHMP will adopt an Opinion which will be forwarded to the European Commission for preparation of a Decision.
In the case of non-fulfilment of specific obligations or follow-up measures, the CHMP will have to consider the possibility of recommending a variation, suspension, or withdrawal of the marketing authorisation.
Table 9 shows the Omnitrope® Risk Management Plan Summary published by EMA.

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Diabetogenic potential of rhGH therapy in short children born SGA	Phase IV prospective, single arm clinical trial in short children born SGA (part of registry reviewing patients' demographics, long term safety and immunogenicity).	Warning regarding diabetic potential in Section 4.4 of SPC*. Rare cases of type II diabetes mellitus in Section 4.8 of SPC.
Occurrence and clinical implications of anti-rhGH antibodies	Phase IV prospective, single arm clinical trial in short children born SGA measuring immunogenicity. Prolongation of ongoing Phase III study EP2K-02-PhIIIlyo to provide long-term immunogenicity data Immunogenicity testing for children enrolled in registry as appropriate (e.g. loss of efficacy).	Development of antibodies included in Section 4.8 of SPC.
Occurrence of malignancies in rhGH treated patients	Registry of patients reviewing patients' demographics, long term safety including malignancy and other safety issues.	Warning in Section 4.4 regarding reoccurrence of malignancy. Leukaemia mentioned as a very rare adverse effect in Section 4.8.
Risks of rhGH treatment in PWS patients	Registry expected to include patients with PWS and will record demographics, long term safety as well as other safety issues in this group.	Warnings on use of rhGH in PWS in Section 4.4. • Respiratory impairment and infection • Sleep apnoea • Severe obesity scoliosis

* SPC Summary of Product Characteristics
Table 9. Omnitrope® Risk Management summary (EMA, 2008)

3.4 Handling of safety concerns

Safety Concerns in the Pre-Authorisation Phase

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

Safety Concerns in the Post-Authorisation Phase

A Drug Monitor, including centrally authorised products, is in place as a tracking system for safety concerns and is reviewed on a regular basis by the PhVWP at its meetings. This summary document also records relevant actions that have emerged from PSURs, specific obligations, follow-up measures and safety variations.
Following the identification of a signal the relevant information needs to be brought together for effective evaluation, over a time scale appropriate to the importance and likely impact of the signal:

- Non-urgent safety concerns
- Urgent safety concerns

3.5 Information to healthcare professionals and the public

The management of the risks associated with the use of biosimilars demands close and effective collaboration between the key players in the field of pharmacovigilance. Sustained commitment to such collaboration is vital if the future challenges in pharmacovigilance are to be met. Those responsible must jointly anticipate, describe and respond to the continually increasing demands and expectations of the public, health administrators, policy officials, politicians and health professionals. However, there is little prospect of this happening in the absence of sound and comprehensive systems for biosimilars which make such collaboration possible. Understanding and tackling these are an essential prerequisite for future development of the biosimilars.
Healthcare Professionals (and the public if applicable) need to be informed consistently in all Member States about safety issues relevant to centrally authorised biosimilar, in addition to the information provided in Product Information. If there is such a requirement the Rapporteur or the Marketing Authorisation Holder in cooperation with the Rapporteur should propose the content of information for consideration by the PhVWP and subsequent discussion and adoption by the CHMP. The agreed information may be distributed in Member States. The text and timing for release of such information should be agreed by all parties prior to their despatch. The Marketing Authorisation Holder should notify, at his own initiative, the Agency at an early stage of any information he intends to make public, in order to facilitate consideration by the PhVWP and adoption by the CHMP as well as agreement about timing for release, in accordance with the degree of urgency. Marketing Authorisation Holders are reminded of their legal obligations under *Article 24(5) of Regulation (EC) No 726/2004* to not communicate information relating to pharmacovigilance concerns to the public without notification to the Competent Authorities/Agency (European Commission, 2004).

4. References

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