# Risk management of biopharmaceuticals: a regulatory perspective

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**Risk management plans aim to facilitate a proactive approach to potential safety concerns by both the marketing authorisation holder and the competent authorities. Within this hospital pharmacists can play an important role in the pharmacovigilance of biopharmaceuticals.**

## Introduction

Since November 2005, new European legislation requires marketing authorisation applicants (MAA) to submit, as part of the marketing application, a description of their proposed risk management system. A risk management system is a set of proposed pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products and also the assessment of the effectiveness of these interventions. The detailed description of a risk management system should be provided in the form of an EU Risk Management Plan (EU-RMP). This is obligatory for all new chemical entities and biosimilars. The submission of an EU-RMP is also required for a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product, and for significant changes in established products (e.g. new dosage form or a new manufacturing process for a biotechnologically-derived product) unless agreed otherwise with the competent authority. Finally, an EU-RMP can be required by the regulators, or at the initiative of the marketing authorisation holder (MAH), when a safety concern with a medicinal product at any stage of its life cycle is identified [1]. This article provides an overview of the requirements of EU-RMPs, the objectives, the implications and explores the possible role of the hospital pharmacist, with a focus on the risk management of biopharmaceuticals.

## Content and objectives of the EU-RMP

The content of the risk management system is laid down in legislation. A guideline and template for the EU-RMP is available via the website of the European Medicines Agency (EMEA) www.emea.europe.eu [1, 2].

An EU-RMP consists of two parts. The first part aims to provide an overview of the results and shortcomings of the performed preregistration studies (laid down in safety specifications) and provides information on actions proposed to follow up the risk-benefit profile (pharmacovigilance plan). Safety specifications summarise the safety profile of the medicinal product at a particular point in time of its

**Table 1: Abbreviations and their meaning**

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| MAA | Marketing Authorisation Applicants |
| EU-RMP | EU Risk Management Plan |
| MAH | Marketing Authorisation Holder |
| RMP | Risk Management Plan |
| EPARs | European Public Assessment Reports |
| GPRD | General Practice Research Database. A computerised database of anonymised medical records from primary care. Currently data are being collected on over 3.4 million active patients (approximately 13 million total) from around 450 primary care practices throughout the UK. It is the largest and most comprehensive source of data of its kind and is used worldwide for research by the pharmaceutical industry, clinical research organisations, regulators, government departments and leading academic institutions. |
| THIN | The Health Improvement Network. THIN is a data collection service that analyses anonymised patient information. The THIN database of anonymous patient information is then accessed worldwide by researchers for medical studies in drug safety, epidemiology and health outcomes. |
| PHARMO | The PHARMO Record Linkage System links patients' medical histories to the use and cost of prescription drugs (pharmacy database), diagnostic/therapeutic data from hospitals, clinical laboratory and pathological findings, GP records and drug histories in hospital. Currently, data are collected from a population of about two million residents in the Netherlands. The PHARMO database provides insight into the use of prescription drugs in daily practice, in particular with respect to effectiveness, safety and the economic value of a prescription drug. |

life-cycle and form the basis for effective and tailored risk management. Safety specifications will be classified as identified risks, important potential risks and important missing information. Identified risks should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility of the adverse events and provide information on at-risk groups, if available. Important potential risks for which evidence has led to the conclusion that there was a potential risk should be further evaluated to characterise the association. Missing information should be studied when considered necessary. The pharmacovigilance plan should describe the (additional) activities a MAH will conduct to further identify, characterise and quantify each safety specification following marketing approval and actual usage in clinical practice. In this part of the RMP additional studies will be proposed.

The second part of the EU-RMP should carefully consider the need for the introduction of risk minimisation activities. For each safety concern, the MAA should assess what is needed to ensure safe and effective use. Risk minimisation activities may be limited to inclusion of appropriate warnings in the product information or by the careful use of labelling and packaging, i.e. routine risk minimisation activities. For other safety concerns, however, additional programmes may be needed, e.g. educational material or training programmes for prescribers, pharmacists and patients or restricted access.

The EU-RMP aims at a proactive approach to the detection and assessment of risk and the concurrent risk minimisation activities in an early stage. The planning of pharmacovigilance activities will be improved and routine pharmacovigilance will be guided to provide prompt investigation of predicted or emerging safety concerns [1]. Summaries of EU-RMPs can be accessed via the website of the EMEA (human medicines, A-Z listing of EPARs, medicinal product, scientific discussion).

## Implications of EU-RMPs

At the time of approval limited data is available on the safety of drugs due to the limitations inherent in clinical trials [3, 4]. Post marketing data offer a valuable complement to clinical studies in evaluating the safety aspect of drugs. Implementation of EU-RMPs has led to the proposal and set up of many observational studies. This counts for both small molecules and biopharmaceuticals. Drug registries have been proposed for biopharmaceuticals in particular since existing databases such as GPRD, THIN and PHARMO (see Table 1) lack sufficient information on exposure and some relevant outcomes.

An example of the more proactive approach of risk management of biopharmaceuticals is the European epidemiological cohort study proposed for Lucentis (ranibizumab). This study will evaluate the adverse events related to intravitreal injections, the systemic effect of VEGF-inhibition (vascular endothelial growth factor), the systemic adverse events related to overdose or bilateral treatment and intraocular adverse events and serious hypersensitivity reactions [5]. Similarly the MAH of Orencia (abatacept) will, for example, initiate a registry in the EU to specifically study infections, infusion related reactions, malignancies, induction/exacerbation of autoimmune disease, the effect of abatacept in paediatric and elderly populations and to study the effect of combination therapy [6]. The value of such registries has already been demonstrated for registries, initiated post marketing, evaluating the safety of biopharmaceuticals for rheumatoid arthritis. A Danish registry covered approximately 90% of the patients treated with biopharmaceuticals and the database picked up 20 times as many safety signals as the mandatory reports to the Danish Medicines Agency [7].

**Hospital pharmacists can provide important information on drug exposure and patient characteristics.**

## Potential role of the hospital pharmacist

Due to the expected limitations of large population-based databases and the use of many biopharmaceuticals in hospital settings, hospital pharmacists can provide important information on drug exposure and patient characteristics. This will provide valuable knowledge on the diffusion and the appropriate use of biopharmaceuticals. Patient characteristics of patients suffering adverse events will (possibly) identify patients at higher risks for the occurrence of adverse events as well. Secondly, information on exposure is important to quantify reported adverse events.

As stated previously the studies proposed within the EU-RMPs play an important role in the identification and quantification of safety concerns. Due to the preparation of most of the biopharmaceuticals by the hospital pharmacy, hospital pharmacists are a valuable source for the formation of cohorts of users. Therefore, hospital pharmacists are encouraged to take part in these studies. Spontaneous reports of adverse drug reactions are a valuable complement to the studies proposed in EU-RMPs for the identification of safety concerns. Hospital pharmacists are therefore encouraged to spontaneously report adverse events to national competent authorities.

## Conclusion

At time of approval limited data is available on the safety of drugs due to the limitations of clinical trials. Therefore, an EU-RMP plays an important role in a proactive approach to identification and management of safety concerns and concomitant risk minimisation activities.

Hospital pharmacists can play an important role in the identification and quantification of patients exposed to the biopharmaceutical. Due to the increasing number of studies proposed in EU-RMPs hospital pharmacists will face more and more studies in future and are encouraged to take part in these studies.


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# Keeping up with pharmaceutical English

This Pharmaceutical English section is to assist you in understanding terminology in EJHP. All the terms defined below can be found in this issue unless otherwise noted.

See pages 69-71

**Ectopic transgene expression:** expression of a characteristic introduced by gene medicine in a target other than that intended. Greater control over the tissue distribution of transgene expression is required to avoid potentially deleterious effects in non-target organs. In this regard, the liver is particularly at risk. Dose limiting toxicity has been seen due to toxic transgene expression.

See page 84 - Production terminology

**Compounding:** Production of a medicine for an individual patient, based on professional experience, knowledge and skill (called "Secundum Artem" or "Lege Artes") of the pharmacist (rather than a validated production protocol).
**Manufacturing:** Large scale production of licensed products.
**Preparation:** Small scale production activities in hospital pharmacies (according to protocol).
**Production:** Production is part of preparation. It involves all processes and operations in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.
**Reconstitution:** The process of adding liquid to a dry powder to restore a solution.

## NEWS FLASH

### Cooperation to improve patient safety

Two complementary global standards organisations will collaborate to advance global automatic identification standards in health care. The aim is to reduce medical errors, enable global traceability and to increase the effectiveness of the healthcare supply chain.

GS1 Healthcare has global standards for automatic identification (through bar codes and radio frequency identification) providing the opportunity to make the healthcare supply chain more efficient and accurate, and thus safer. Medication errors can be avoided by automatically matching product data to patient data. These standards also enable effective traceability and reduce counterfeiting.

ICCBBA is a not-for-profit information standards body that manages the well established ISBT 128 information standard widely used for the coding of human blood, cellular therapy and tissue products. ISBT 128 improves safety and supports traceability around the world by providing a globally unique identifier for transfusion and transplantation products, and a coding system for these products based on internationally agreed reference tables.