



Harmonising Safety Reporting

Consultant Stephen A Goldman gives an insight into effective pharmacovigilance planning and risk management in an evolving global regulatory environment

Pharmaceutical safety is a continuum that begins with preclinical animal testing, continues throughout human clinical trials and up to market approval. However, rather than ending with its emergence on the market, performing ongoing surveillance and assessment of new safety information is critical to mitigating and managing the potential of a pharmaceutical (drug or biologic) for adverse effects in patients, and overall public health. Thus, planning for how pharmacovigilance is to be performed upon approval, as well as constant re-evaluation of a product's benefit/risk profile throughout its life cycle, are of great necessity.

Towards this goal, multinational initiatives conducted under the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use auspices, along with the Council for International Organizations of Medical Sciences (CIOMS) and other regulatory-related projects, have attempted to foster a consistency of approach and accepted practices industry-wide. At the same time, exciting advances in clinical pharmacology, pharmacogenomics and pharmacogenetics have added to the knowledge of how individual patients may respond to pharmaceutical agents, and valuable insight into the natural history of varied diseases has been gained through expanded use of pharmacoepidemiology techniques.

Postmarketing pharmacovigilance and risk management are now truly global; therefore, understanding national and international approaches to signal detection, case evaluation and risk mitigation is of critical importance. Just as significant is understanding the methods used to communicate risk information to healthcare professionals and consumers, and how the effectiveness of risk management programmes is to be measured.

This article will examine current perspectives in two of the main ICH regions (US and EU) and approaches to pharmacovigilance planning and risk management throughout the medical product life cycle, from clinical trials to product approval to marketing. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory requirements and standards, in combination with ICH guidelines, will be discussed along with examples of risk assessment and minimisation methods and the challenges that the industry faces in performing high-quality risk management in a global environment.

FDA TASK FORCE

In 1998, an FDA task force was established to assess the system for managing risks associated with the use of FDA-approved medical products. The task force was asked to concentrate on the FDA's role in three basic areas: quality of its premarketing review and risk assessment; strengths and weaknesses of the agency's postmarketing surveillance and risk assessment; and other the FDA risk assessment activities. The resulting May 1999 report to the FDA Commissioner was a landmark document that established FDA's philosophy in this regard (1,2). In combination with international safety-related initiatives under ICH (for example, the E2A Guideline) and CIOMS (for example, CIOMS IV), the task force report provided a framework for the FDA's ongoing programmes and initiatives for safe use of medical products with both national and global applicability (3,4).

The task force examined all FDA risk management activities within the context of the entire healthcare delivery system. Further, by assessing the FDA's role in both pre- and post-marketing phases, the task force fostered the critical concept of risk management being a continuum spanning all phases of a medical product's life cycle.

In its report, the task force emphasised that responsibility for risk management of medical products used in the US does not rest solely with the FDA, but is shared by the FDA with industry, healthcare professionals, patients, other federal groups, healthcare delivery systems and professional organisations.

SAFETY REPORTING: NEW RULE

The report's influence on the FDA's risk management programmes is apparent in regulatory actions taken in relation to the unsafe use of marketed pharmaceuticals, such as co-prescription of known contraindicated drugs, and its emphasis on monitoring pharmaceutical benefit/risk profiles in the 2003 safety reporting Proposed Rule (5,6). Its effect outside the US is unclear – while barely mentioned in the 2001 Summary Report of the Heads of Agencies Ad Hoc Working Group, both reports have common concerns and provided recommendations for enhancement of public health in relation to risks associated with medication use (7).

Under the 2003 Proposed Rule, currently mandated postmarketing expedited submission of serious, unexpected

adverse events and associated follow-up information within 15 calendar days would also require expedited reporting of information sufficient to consider changes in administration of a marketed pharmaceutical based on appropriate medical judgment, encompassing significant unexpected *in vitro*, animal or human (clinical; epidemiological) study safety findings or aggregate data from studies suggesting significant risk to humans (for example, mutagenicity, teratogenicity or carcinogenicity) (6). While this paradigm is considered start-of-the-art, and is consistent with Volume 9A of the rules governing medicinal products in the EU, it remains a proposed rule in the US (8).

This is in contrast with clinical trial safety reporting, as the FDA released investigational new drug safety reporting requirements for human drug and biological products in September 2010 – this rule became effective on 28 March 2011 (9).

The new rule requires reporting of serious, unexpected, adverse drug reactions for which “there is evidence to suggest a causal relationship between the drug and the adverse event”. In an effort to enhance safety signal detection, examples are given as to when a single event should be reported (for example, uncommon events known to be strongly associated with drug exposure), when there is need to wait for more than one occurrence, and aggregate analysis of specific events (9,10).

In addition, other safety information now to be reported to the FDA within 15 days of becoming aware of an occurrence includes findings from clinical or epidemiological studies suggesting significant risk to study participants; serious suspected adverse reactions occurring at higher than expected rate; and serious adverse events from bioavailability studies which determine what percentage and at what rate a drug is absorbed by bloodstream, and bioequivalence studies which determine whether a generic drug has the same bioavailability as a brand name drug.

Under the new rule, definitions and reporting standards have been revised for greater consistency with ICH and CIOMS so as to help ensure harmonised reporting of globally conducted clinical trials.

RISK MINIMISATION

This finalised IND reporting rule is the latest component of the FDA's risk management activities. In 2005, the FDA published three risk minimisation guidances: ‘Premarketing Risk Assessment’, ‘Development and Use of Risk Minimization Action Plans [RiskMAPs]’ and ‘Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment’ (11).

Regarding RiskMAPs, routine risk minimisation measures – such as periodic updating of FDA-approved professional labelling to incorporate information from postmarketing surveillance or studies revealing new benefits or risk concerns – along with good reporting practices, were thought by the FDA to be sufficient for most products, without the

need to consider a RiskMAP (12). A RiskMAP is a strategic safety programme designed to meet specific goals and objectives in terms of minimising a product's known risks, while preserving its benefits; one or more safety-related health outcomes or goals is targeted, and one or more tools is used to achieve the goals set out. Tools that can be used to achieve RiskMAP goals and objectives were classed into three categories: targeted education and outreach; reminder systems; and performance-linked access systems.

Targeted Education and Outreach

These tools include healthcare practitioner letters, training programmes for healthcare practitioners or patients, continuing education for healthcare practitioners, prominent professional or public notifications, and patient labelling such as medication guides and patient package inserts.

With respect to tool effectiveness, major categories of perceived risk (drug-drug interactions, off-label use, recommended blood test monitoring and teratogenicity) must also be part of the evaluative process – as behaviours associated with each category of risk may differ, so may communication methods utilised optimally (5). Multiple modes of risk communication and maximal publicity can heighten overall effectiveness; further, in assessing effectiveness of risk communication, desired results must be clearly stated, as a fair degree of achieved success may not be seen as effective enough to prevent market withdrawal of the pharmaceutical product.

Reminder Systems

When targeted education and outreach tools are insufficient to minimise risks, reminder systems tools are recommended for additional use. Examples include healthcare provider training programmes; testing or other documentation of physician knowledge and understanding; enrolment of physicians, pharmacies and/or patients in special data collection that reinforces appropriate use; and specialised systems or records attesting to safety measures having been satisfied (for example, prescription stickers and physician attestation of capabilities).

Performance-Linked Access Systems

When routine risk minimisation measures, targeted education and outreach tools, and reminder systems are insufficient to minimise risks, and products have significant or otherwise unique benefits in a particular patient group or condition, but unusual risk – such as irreversible disability or death – also exists, then performance-linked access systems are recommended for use. These include systems that link product access to laboratory testing results or other documentation, such as a sponsor's use of compulsory reminder systems, prescription only by specially certified healthcare practitioners, dispensing only by pharmacies or practitioners that elect special certification, and dispensing only to patients with evidence or other documentation of safe-use conditions (for example, lab test results). A successful example of the latter is the programme for clozapine and agranulocytosis (13,14).

The RiskMAP and the other two minimisation guidances are high quality and of great utility in the US and abroad, but RiskMAPs remain under a guidance, having not been incorporated into rules or regulations.

PHARMACOVIGILANCE PLANNING

The same situation exists in the US regarding the influential ICH guideline, ‘E2E: Pharmacovigilance Planning’, crafted to foster international harmonisation and consistency, especially in the early postmarketing period of a new drug or biologic (15). Its underlying principles are: planning pharmacovigilance activities throughout a product’s life cycle; a science-based approach to risk documentation; effective collaboration between regulators and industry; and applicability of the pharmacovigilance plan across ICH regions. The guideline focuses on a safety specification and pharmacovigilance plan that might be submitted at the time of application for marketing authorisation, with an annex describing pharmacovigilance methods. The safety specification is a method for summarising important identified and potential risks and missing information, including potentially at-risk populations and situations where the medical product is likely to be used that were not studied pre-approval. Thus, by using the premarketing safety database and available worldwide experience and scientific literature, factors that might affect the product’s benefit/risk balance are identified for further evaluation.

The guideline also provides a proposed pharmacovigilance plan structure and principles of good practice for design and conduct of observational studies, but does not describe other methods to reduce risks from products, such as risk communication. While not covering the entire scope of pharmacovigilance, E2E encompasses the use of pharmacoepidemiological studies, and is most useful for: new chemical entities, biotechnology-derived products and vaccines; significant changes in established products; and established products to be introduced to new populations, with significant new indications, or when a new major safety concern has arisen.

The pharmacovigilance plan should be based on the safety specification and can be written as two parts of the same document. Normally developed by the sponsor, it can be discussed with regulators during product development, prior to approval (when marketing application submitted), or when a safety concern arises postmarketing.

Continuous monitoring of the product’s safety profile, through signal detection, issue evaluation, label updating and liaison with regulatory authorities is considered standard as part of ‘routine pharmacovigilance’ – this is in keeping with the 1999 FDA Task Force Report, 2001 EU Summary Report of the Heads of Agencies, and the FDA’s 2003 Proposed Rule.

E2E was operationalised in all three ICH regions in 2005 – however, the approach taken in Europe differs from that in the US. The then EMEA’s ‘Guideline on Risk Management

Systems for Medicinal Products for Human Use’ went into effect in November 2005 with an EU Risk Management Plan (EU-RMP) that utilised E2E concepts and language – the guideline was later incorporated into Volume 9A (16).

Circumstances when an EU-RMP is required are consistent with E2E, and consists of two elements:

1. Part I: Safety Specification and Pharmacovigilance Plan (as in E2E), with additional EU requirements as to potentials for overdose, transmission of infectious agents, and misuse for illegal purposes in the safety specification
2. Part II: Evaluation of need for risk minimisation activities – if there is need for additional (non-routine) risk minimisation activities, RMP also includes risk minimisation plan that includes both routine and additional risk minimisation activities

The guideline’s ‘Annex A: Epidemiological methods for PASS [post-authorisation safety studies]’ is in line with E2E, with ‘Annex B: Methods for Risk Minimization’ having elements in common with FDA’s RiskMAP guidance. Annex C, the EU-RMP Template, was released in September 2006 as a separate document. Under the guideline, an EU-RMP is to be submitted with an application for a new marketing authorisation, or an application entailing a significant change in a prior marketing authorisation.

RISK EVALUATION & MITIGATION

The situation is different in the US – there are no corresponding FDA regulatory requirements for submission of a safety specification and pharmacovigilance plan with every new application for pharmaceutical marketing authorisation, and RiskMAPs remain under guidance. However, in September 2007, the FDA Amendments Act (FDAAA) was signed into law, with a new category of mandatory risk management plan enacted: risk evaluation and mitigation strategies (REMS) (17).

REMS, under FDAAA, are quite similar to RiskMAPs, as both are needed only when judged necessary by the FDA in order to ensure that a drug’s benefits outweigh its risks, and the same criteria are to be used to make that determination looking at aspects such as, the seriousness of the disease or condition to be treated and the expected benefits of the drug. If a REMS is not required when an application is approved, it may subsequently be required (including the FDA acting on supplemental application for new indication) if there is awareness of new safety information, and determination made that a REMS is necessary to ensure the drug’s benefits outweigh risks.

Of the original list of drugs and biologics approved before FDAAA provisions took effect on 25 March 2008 deemed to have REMS, all had RiskMAPs in place prior to that determination (18). Drugs and biologics approved before this

date that only had a medication guide and no elements to assure safe use (ETASUs) as defined in FDAAA, were not deemed to have REMS under FDAAA. With respect to enforcement under FDAAA, there are civil monetary penalties for violations of REMS provisions, or a drug or biologic can be deemed misbranded and FDA could obtain injunctive relief.

In September 2009, the FDA released a draft guidance stating that many of the principles in the RiskMAP guidance were embodied in FDAAA REMS provisions as implemented by the FDA (19). The RiskMAP guidance continues to apply to products with existing RiskMAPs (for example, those not deemed to have an approved REMS in effect) and those with new RiskMAPs (such as ANDAs for which reference listed drug has RiskMAP). Products previously approved with a medication guide or patient package insert that meets statutory requirements for REMS will now be required to have REMS, and the draft guidance reiterates that REMS are subject to inspection and enforceable. The content of a proposed REMS includes the product and contact information, goals, additional potential REMS elements, ETASUs, an implementation system, and a timetable for submission of assessment of the REMS. The content of a REMS supporting document includes background, goals section, supporting information about proposed REMS elements, REMS Assessment Plan, and other relevant information.

As for new developments in the EU, there is an ongoing EMA benefit-risk methodology project, which started in early 2009 and is scheduled to run until the end of 2011. It has five steps and is being conducted in collaboration with academia such as experts in decision theory from the London School of Economics and Political Science, and with the University of Groningen. Through this project, the EMA aims to make its decision-making on the benefits and risks of medicines more transparent, more consistent and easier to audit (20).

To date, two work package reports have been released. The first (in March 2010) provided a description of the current practice of benefit-risk assessment for centralised procedure products in the EU (21). In the second (from August 2010), approaches for balancing benefits and risks in decision-making about medicinal products were reviewed, with perceived usefulness to regulators in making pre- and post-approval decisions completing each review (22).

NEW AMENDMENTS: EU

With respect to regulation, on 22 September 2010 the European Parliament adopted a proposal for a regulation and directive amending, as regards pharmacovigilance, regulation (EC) 726/2004 and 1394/2007 Directive 2001/83/EC of the Community code relating to medicinal products for human use which was published in the Official Journal of the EU on 31 December 2010 (23). This Directive enters into force on the 20th day following its publication in the *Official Journal of the European Union* (that is, Sunday 20 January 2011), but member states have until 21 July 2012

to adopt its provisions. The regulation is not due to come into force until 2 July 2012. Among the amendments which reinforces existing requirements are that:

- ◆ The marketing authorisation holder (MAH) should establish a pharmacovigilance system to ensure monitoring and supervision of one or more of its authorised medicinal products, recorded in a pharmacovigilance system master file permanently accessible for inspection. A summary of the pharmacovigilance system should be submitted with the marketing authorisation application and include a reference to the site where the pharmacovigilance system master file for the medicinal product concerned is maintained and accessible for inspection by the competent authorities.
- ◆ Planning of pharmacovigilance for each individual medicinal product by the MAH should take place in the context of a risk management system and should be proportionate to identified risks, potential risks and the need for additional information on the medicinal product. It should also be ensured that any key measures contained in a risk management system are included in the marketing authorisation as conditions.
- ◆ National competent authorities are to make publicly available the marketing authorisation, package leaflet, summary of product characteristics (SmPC) and any deadlines for fulfilment of conditions where necessary for each medicinal product which they have authorised – the public assessment report shall include a summary written in a manner understandable to the public.
- ◆ MAHs can be required to conduct post-authorisation studies on safety and efficacy at time of marketing authorisation or later, and it should be part of marketing authorisation.
- ◆ All medicinal products with a new active substance and biological medicinal products including biosimilars for which pharmacovigilance activities are prioritised are authorised subject to additional monitoring. This may also apply at the request of competent authorities to specific products, subject to requirement to conduct a post-authorisation safety study or where there are conditions or restrictions with regard to safe and effective use of the medicinal product.
- ◆ Products subject to additional monitoring should be identified by a black symbol and corresponding explanatory sentence on SmPC and patient information leaflet.
- ◆ In order to increase transparency on pharmacovigilance processes, member states should create and maintain medicines web-portals. To the same end, MAHs should provide authorities with prior or simultaneous warnings about safety

announcements and authorities should provide each other with such warnings.

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