Risk Management:

The Move to Implementation

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Talked about for decades, in the post-Vioxx® era, pharmacovigilance activities have finally brought risk management to the forefront. Management of risk holds different meanings for regulators and drug manufacturers; however, in the end, it is patient safety which is paramount.

The current system of drug regulation is a relatively recent phenomenon, dating from the 1950s in most Western countries. The system has mainly been designed to perform the function of approving a molecule for sale and distribution, often as a one time event. Not much thought went into further monitoring outside of systems to collect voluntary, spontaneous Adverse Event (AE) reports. The effectiveness of such a system has been crude at best, with catastrophic events required before any regulatory action was taken. In general, this system of risk management, if the term "management" can even be used, contributed very little to the understanding of patient risk, both qualitatively (*i.e.*, susceptibility factors, extent and duration of risk) and quantitatively (*i.e.*, actual numerical data on risk vs. benefit). Now, regulatory agencies are aggressively taking a greater interest in regulating an approved product throughout its life cycle, not simply authorizing its access into the market. This trend is global, hopefully fostering an environment of greater standardization and cooperation.

Regulating bodies worldwide are issuing guidance documents on pharmacovigilance, both internal and external policy statements on risk management and using their regulatory muscle to enforce transparency in the activities and communications of a somewhat beleaguered pharmaceutical industry. By obligating pharmaceutical manufacturers to follow, in effect, regulators are practicing organizational risk management by assuring their organizational goals of patient safety are satisfied. Furthermore, by removing the voluntary nature of these activities, the playing field has been leveled for pharmaceutical companies, reducing the somewhat perverse disincentives that exist in a spontaneous AE reporting system.

In the US, the FDA's Centre for Drug Evaluation and Research has issued their *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* which outlines its strategies for the pre- and post-marketed product. Even though these are not legally enforceable, they do provide clear direction on signal detection, signal interpretation and pharmacovigilance plans. The FDA's risk management guidance incorporates risk assessment in the pre- and post-marketing scenarios, as well as risk minimization. Similarly, the European Union (EU) has forged even further ahead by mandating compliance and penalizing companies for non-compliance with EU regulations and not satisfying their obligations. *Guidelines on Pharmacovigilance for Medicinal Products for Human Use*[1] is an extensive document detailing specific mandated requirements for:

- pharmacovigilance systems,

- monitoring of compliance,
- risk management systems,
- reporting,
- signal detection and
- communications activities.

The European Medicines Agency (EMEA) is responsible for "in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation."[1] The EMEA has a scientific committee, The Committee for Medicinal Products for Human Use, within which is the Pharmacovigilance Working Party (PhVWP). The role of the PhVWP "is to provide advice on the safety of medicinal products and the investigation of adverse reactions, in order to enable effective risk identification, assessment and management, in the pre- and post-authorization phase."

Similarly, Health Canada (HC) has taken a stand. In an environment of increasing priority reviews and Notice of Compliance with conditions (NOC/c), HC has plans to implement processes which monitor beyond the approval process. The number of NOC/c granted by HC has increased over the past years from four in 2004 and 2005, to seven in 2006 and three in the first quarter of 2007 alone. Most of these have been eligible for receiving an NOC/c because the molecules were indicated for oncology or other life-saving conditions. With an NOC/c, HC authorizes early market access of a promising drug, contingent upon the sponsor undertaking additional studies to support clinical benefit and enhanced post-market safety surveillance steps.

As such, HC's role has "been evolving from the traditional gatekeeper role of the past to include roles such as information provider and risk manager."[2] With this evolution, HC has reacted with the Progressive Licensing Framework (PLF), part of HC's Blueprint for Renewal initiative which is an attempt to modernize the regulatory environment moving forward.

The foundation of the PLF is that knowledge and understanding of a drug occur over time and not at one point in time. The drug's safety profile is not completely known or available pre-market approval. The framework offers a three pronged methodology:

1. A life cycle, evidence-based approach which will enable sound decision making on a scientific basis throughout the life cycle of the drug
2. Good planning which would enable "a proactive approach to managing both expected and unexpected issues."[2] Pre-marketing filing with HC will become more detailed with earlier involvement and evaluation of clinical trial methodologies, protocols, anticipated manufacturing changes and planning for post-market activities, such as future studies, monitoring plans, surveillance strategies and risk management for the drug
3. Accountability would rest with both HC for licensing the drug and the drug manufacturer throughout the life cycle of the drug

Internally, at the organizational level, HC has a strategy to implement an Integrated Risk Management Framework to provide a "continuous, proactive and systematic process for understanding, managing and communicating risk from an organization-wide perspective."[3] It has further developed a Strategic Risk Communications Framework[4] to support its risk management processes.

Barriers to post-marketing surveillance

Barriers exist to post-marketing surveillance. Lack of awareness of processes, lack of commitment and quality of data submitted on reports have all been cited as challenges in drug safety monitoring in the post-marketing environment. To combat these challenges, drugs with potential or identified safety risks have had risk management requirements mandated by regulators through various mechanisms, such as post-marketed registries. Examples include Revlimid® in the US and Iressa® in Canada, with more drugs in the pipeline which will have to satisfy stricter requirements for initial and continued availability in the respective market.

Yesterday, regulators made drugs available in the market. Today, regulators are following the drug beyond approval. There is a strong move towards greater engagement by regulators in

the life cycle of drugs which means a shift towards an era of fostering collaborative partnerships between regulators and pharmaceutical manufacturers. CPM

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McKesson Specialty Pharmaceutical Solutions is a division of McKesson Canada that offers outsource medical information, medical writing, pharmacovigilance and direct-to-patient services to the pharmaceutical industry.

Announcement

Rx&D Announces Ronnie Miller as Chairman of Board of Directors

Ronnie Miller, President and CEO, Rx&D

Canada's Rx&D is pleased to announce the appointment of Ronnie Miller, President and CEO of Hoffmann-La Roche Limited (Roche Canada) as Chairman of the association's Board of Directors.

Mr. Miller is a member of Rx&D's Executive Committee and Board of Directors. Until becoming Board Chairman, he served on several industry committees including Public Affairs, Stakeholder Relations and, more recently, as Chair of the Rx&D Federal Affairs/FPT Relations Standing Committee.

Mr. Miller has over 28 years of extensive and varied experience in the pharmaceutical industry. He began his career in the UK as a sales representative and held a series of progressive positions including Sales Management, Product Management, Business Unit Director and National Sales Manager.

In 1988, Mr. Miller joined Roche as National Sales Manager for Roche Products Ltd. in the UK. In 1992, he moved to Roche's head office in Basel, Switzerland, as the International Product Manager for Neupogen®.

From 1993 to 1996, he worked for Roche in Japan as Marketing Director and Deputy Divisional Director of the Pharmaceutical Division. In 1996, he moved back to Roche's global head office in Basel, to lead the global task force for Xenical®. Mr. Miller returned to the UK in 1997 as Divisional Director of Pharmaceutical and remained there until April 2000, when he was appointed to his current position as President and CEO of Roche Canada.