

Fundamentals in Drug Safety Strategies

John McLane, Ph.D.

Clinquest, Inc.

Risk and Benefit management processes have become exceedingly complex in today's drug development environment. Starting from the preclinical assessments to the full Risk Evaluation and Mitigation Strategies (REMS) for the Safe Use of pharmaceutical products, risk management has become integrated into our development programs. Although there has been increased emphasis and new laws and guidances on Risk Management Plans and REMS programs, we have been pursuing these programs in our industry for years and improving our methods continuously. All of the drug development non-clinical and clinical studies and the CMC procedures already in place have a critical role in providing data for assessing the risks and benefits of a medical product. However, as has been pointed out in numerous publications, editorials, and comments, we can continue to improve on reaching our goals to ensure that medical products have an acceptable safety and benefit profile and that health care providers and patients can make well informed decisions to use or not use the product. In order to improve these processes, we need to build from a solid foundation based on the principles of protecting the public health. The key to developing a successful risk management program begins with the establishment of a comprehensive and workable plan that has the organization's full support and includes training personnel in the risk management functional groups and throughout the entire organization. Just as a coach for a professional team develops strategies and plays appropriate for the situation, they also assure that the fundamentals are in place for each of the players.

The fundamentals to manage this core of risk management activities are:

- Develop a comprehensive Risk Management Plan for each project/product
- Implement written policies and procedures to provide guidance to the organization
- Designate a lead officer/manager
- Assure effective and defined lines of communication
- Provide a mechanism for periodic monitoring and auditing of the plan
- Respond promptly to identified issues
- Provide effective training and education

The fundamental core of any risk management plan is the continuous improvement process circular diagram we are familiar with from the Summary of Pharmacovigilance Systems (SPS), Quality Risk Management (Q9) and Risk Minimization Action Plans (RiskMAPS) Guidance documents. The process starts with the collection of data, but this data collection is active throughout the life cycle of the product - starting with the preclinical assessments and continuing through the Post-marketing surveillance activities. The process is expanded with the use of additional tools to develop risk assessments, risk

controls, risk and benefit communication, and assessments for evaluating the utility of the tools that generate the feedback that is employed to reassess the risk and benefit profile.

Although we are becoming more sophisticated in using the different algorithms and analytical tools for risk identification, analysis and evaluation, and we are learning some of the elements that might lead to better communication; the collective changes needed to implement Risk Management Programs require a core cultural thought process. For all of the processes and tools to be effective, each individual on every team needs to have a basic understanding of Pharmacovigilance (PV) concepts, risk management personnel need to have a substantial knowledge of PV concepts, and the organization needs to achieve active committed participation.

Within a company, the development and championing of Risk Management Programs have to be a part of the overall mindset and organizational structure, whether they are part of the layered organization within an international pharmaceutical company or the flat structure of a virtual startup. The development of SOPs, policy statements and integrated standardized work orders is the start of assuring that the organization understands the necessity of the plans. A key component of success of risk assessment is to assure that risk management is integrated into even the early stages of a product's life cycle. The integration means that there are processes and systems in place to assess the identification of issues, procedures for documentation and communication, and procedures to take appropriate action.

Every organization is balancing projects and products against risks and quality, time and cost. The functions of data collection, analysis, and interpretation, whether for an investigational or a marketed product, are usually separated from the strategic management groups that make the continuing development decisions and from those clinical and marketing groups that need to communicate the risks and benefits to the users. Therefore, the functionality of the risk management program within an organization must be based on the concepts of leadership, communication, and the training and commitment of the employees.

One of the key drivers in assuring continuous compliance with the fundamentals is to define a leader and champion for the risk management process. The EU requirements for a Qualified Person for Pharmacovigilance (QP-PV) provide the framework for the qualifications of such a champion, even in small companies:

- Establish and maintain a risk management system including all activities which contribute to the detection, assessment, understanding and communication of safety information, as well as risk management activities
- Oversee the safety profiles and any emerging safety concerns
- Act as a single point of contact for internal and external communication

In some companies, the Chief Medical Officer may function in this leadership role during developmental projects. Because of the conflicting responsibilities, a project manager would not be a good candidate for this role even though s/he may be the overall

champion for the project. In companies with an EU presence and marketed product, the QP-PV has a much greater responsibility and functions in a highly “regulated” position. Within virtual companies with products under development, this role could be outsourced to an experienced contracted Medical Officer.

The fundamental organizational strategy is to develop a communication and decision process that serves to identify the situations that lead to risk; determine if the risk is preventable; and, decide if action is warranted, and if so, how to proceed to prevent and mitigate the situation. Within many large pharmaceutical and medical device organizations, risk management processes are in place. These processes may include preclinical and clinical safety committees that have clear communication channels to all functional groups and are empowered to strategically evaluate issues in a larger context and make corporate level decisions. However, in smaller organizations, and in those companies that often outsource projects, the focus on risk management issues during development or after approval may shift to additional organizational priorities and the communication channels for risk assessments can be damaged. That is to say, on a project or product team, the processes to bring issues to the forefront may not be clearly delineated. It is therefore necessary for smaller companies to focus on assuring that there is an appropriate understanding of risk management concepts and providing training for their employees and their contractors. Operating under this paradigm, an organization will be able to ensure that equal attention will be given to the activities of assessing and communicating risk issues in relation to the other components of the projects. A key economic driver in getting to this surety is reaching critical inflection points for a project. The review, which occurs during portfolio review or during the due diligence phase of the projects provides a clear and concise understanding of the risks and benefits, and confirms that there are not gaps in the risk collection and assessments completed up to that point in the product development process. Accordingly, the drug development process must incorporate early thinking and planning for risk management, integrating risk management with good communication, and a commitment to risk management in the early stages of the product lifecycle.

Quality Control (QC) and Quality Assurance (QA) are obviously key components of our projects and products. Many companies are prepared for audits and inspections on our CMC and clinical programs; but, how many are really ready for audits on our PV programs - particularly when you are in the pre-market stages? As with any process, the procedures and methods need to be transparent and documented. Our regulations essentially require that data can be tracked to the source, and that we write integrated safety summaries of risk issues based on the evidence. To be prepared for a PV audit and to have the risk management procedures already in place during the pre-marketing phase will assure a smoother transition during the market approval process. As many of you know, the formal FDA request for a REMS program may not come (actually, is not likely to come) until the NDA review process is well underway. Since preparing a REMS program requires a reassessment of the risk evaluations conducted to date, the preparation for this may include an internal and/or independent inspection or audit of the data and processes. While planning for this exercise, a company needs to recognize that not all

auditors are equal. A QC/QA auditor that has only conducted clinical or CMC audits may not be familiar with the distinct elements of PV and may not be able to detect the issues and gaps as effectively as an auditor or auditing company that is familiar with PV and safety surveillance activities, and is experienced with risk management and assessment procedures.

As a product moves into the later stages of development, the PV processes also need to evolve. PV primarily involves the collection, identification and evaluation of safety signals in the population using the medical product. Pre- and Post-marketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk evaluations and minimizations. The human factor and ability to assimilate information is important in determining which safety signals may represent a concern due to an excess of adverse events in comparison to what would be expected to be associated with a product's use. As we know, after a signal is identified, it should undergo further analysis to determine whether it represents a potential safety risk and whether other action should be taken. As identified in the Q9 guidance, even a single well documented case could be a signal. A thorough case review and case studies, as well as the periodic safety reports we generate, all need to be scrutinized by the critical eye of a well trained professional.

The next fundamental competency is not process-based, but is one we must pay particular attention to in order to have a successful risk management program: Employ or contract qualified professionals. Where do our PV specialists come from, and what training are they undergoing to develop their experience and critical judgment skills? Training on SOPs is not sufficient. What would you look for in your PV hires and how would they be trained?

Regulations require that employees are trained to perform their duties, but have not specified the level of training required. Employees involved in implementing risk management programs need appropriate biological/medical background including medical terminology, and need to have knowledge of general drug development, regulatory reporting criteria, Pre-marketing and Post-Marketing PV event assessment and case processing, adverse event medical coding, drug specific training including drug class data, drug specific biological background, and geographical PV/Medical Information (MI) regulatory knowledge. A solid PV training program is designed to provide employees with the knowledge and skills for providing PV “best practice” services for all types of pharmaceutical and medical device products and companies.

At the conclusion of a robust PV training program, the employee should be able to accurately assess drug or device safety information for seriousness, labeled/ listed/expectedness, and reportability; enter that information into a computer safety database; code adverse events and medical history terms; write objective narratives summarizing the clinical course of the patient/subject; and prepare reports for submission to regulatory agencies. In our regulated environment, we need to practice the

fundamentals of drug safety. Risk management plans are the new rule, and our PV Specialists need to be:

- Informed of the environment in which the pharmaceutical industry operates and the current trends and business issues;
- Knowledgeable on the relevant regulations and codes of PV practice;
- Aware of the basics of drug and medical device safety information management including different media and methods for retrieval and analysis of safety and pharmaceutical information;
- Adept in the processing of clinical and post-marketing PV adverse event reports;
- Competent in the collection and data entry of safety information and in the provision of the required regulatory reports;
- Able to provide safety information and reports to management, internal clients, external clients, business partners, and the FDA/EMA; and
- WELL PREPARED.

Please feel free to contact Clinquest, Inc. to discuss solutions to address these fundamental issues:

John McLane, Ph.D.
Vice President Clinical and Regulatory Affairs
Clinquest, Inc.
One Cabot Road
Hudson, MA 01749

www.clinquest.com
jmclane@clinquest.com

(978) 568-4085
(401) 921-0031

