Final Business Plan
Q9: Quality Risk Management
Dated and endorsed on 11 November 2003

Background

Although risk management approaches to product quality and GMP are routinely applied, at least empirically, by both industry and regulators in every ICH region, there is currently no comprehensive document which describes principles for how risk management should be effectively applied and consistently implemented into decisions regarding product quality which may have an impact on patients. Even within a single region or country, industry and regulators adopt different approaches to risk management and these differences are magnified if viewed across the different ICH regions.

As part of ICH discussions in July 2003 on optimising management of product quality in a global context, a consensus vision statement was agreed by all parties and observers:

Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasising an integrated approach to risk management and science

The integration of risk management into the pharmaceutical quality system is an important component of this vision.

The absence of a harmonised approach to risk management leads to the following problems and inefficiencies:

- Pharmaceutical products may not be available to patients when needed, e.g. when a product is recalled from a market or where different risk decisions contribute to inefficient manufacturing processes and consequent delays
- May increase the potential for the release of unacceptable product to the market
- Delays may occur during implementation of changes and improvements to processes
- Safe and effective drugs may be discarded or recalled from the market
- Manufacturers may be reluctant to implement new technologies or continuous improvements to products or processes
- Scarce resources may not be optimally allocated
- Lack of appropriate date to evaluate risk most effectively

Proposal

In order to develop a harmonised approach to risk management in the area of pharmaceutical quality, it is proposed to set up an ICH expert working group including expertise from risk management, quality, and regulatory and manufacturing fields to develop a harmonised tripartite guideline. Since this will be a guideline with broad applicability, representatives from WHO, the OTC industry, and the generic industry will be invited to participate.

This guideline will define how principles of risk management can be more effectively applied and consistently integrated into decisions by regulators and industry regarding the quality of pharmaceuticals across their lifecycles, i.e. from initial product development through optimisation of manufacturing and control through post marketing changes.

This guideline will include a framework for risk management for pharmaceutical quality which will contribute to more consistent science-based, decision-making and which will support the establishment and vision of quality related practices, guidelines, requirements and standards.

The text book definition of risk management is "a process consisting of well-defined steps which when taken in sequence, support better decision making by contributing to a greater insight into risks and their impacts. Risk management includes elements such as risk identification, assessment mitigation, elimination and communication."

The guideline will address at least the following issues:

- A common terminology, including a definition of quality, risk, risk management etc
- Definition of principles for how risk management can be effectively applied and consistently integrated into decisions regarding product quality
- Operationalisation of the integration of risk management into the decision making process
- Definition of criteria on how to apply the risk management process
- Identification of circumstances, if any, when applying risk management principles is not feasible or appropriate
- Defining what principles of risk management apply to industry, regulators or both across the life-cycle of the product
- How, what and when information is exchanged between and within industry, to the regulators, and to both, throughout the product life cycle
- Synergies with the pharmaceutical development project
- Definition of roles and responsibilities of regulators and industry, including communication responsibilities
- How risk can be incorporated into resource allocation decisions

Benefits of such an approach

The strategic drivers for this proposal are the benefits expected for all ICH parties and observers. Such a guideline would be expected to have the following benefits:

- Enhancement of patient confidence worldwide in decision making on the quality of pharmaceuticals
- Promotion of more effective use of regulatory and industry resources
- Establishment of a systematic, well-informed and thorough method of decision making which leads to greater transparency and predictability
- Increased knowledge of exposure to risk
- Fostering continuous improvement and quality by design generally leading to enhanced product quality

Effort required

It is anticipated that such a harmonised guideline (to step 2) could be developed within a 12 month period, assuming input of 12 man days per ICH sponsor for essential meetings over this period and 15 man days of input from an appointed Rapporteur. Additional input would be expected from observers. Progression to step 4 is anticipated to be less resource intensive.

Cost-benefit of this proposal

It is difficult to estimate the real cost benefit of such a proposal, but, to take one example, the hosting of a single (non-complex) GMP inspection typically requires input of at least 8 man-days by industry and 8 man-days by a regulatory team.

If the results of a risk management guideline saved the equivalent of ten regulatory inspections for the whole of the pharmaceutical industry, the cost of developing the guideline would have been offset.

Apart from reduced numbers and duration of inspections, significant other resource savings are expected from reducing reviews of application changes, better allocation of resources, fewer product recalls… For example FDA alone reviewed over 1000 prior approval review supplements in 2002, at an average of over 20 man-hours per review (rough estimates).

Facilitating the introduction of new technology sooner allows industry to recoup its return on investment more efficiently. In addition improved international communication on significant risks will have positive public health impacts, result in enhanced patient safety and facilitate consistent international approaches.

Substantially higher saving of resources than the one example illustrated can be anticipated for both industry and regulators, therefore the expected benefits are anticipated to greatly exceed the costs.

Additionally, savings for the industry are significant as well with the reduction of inventory costs incurred when having to wait for a prior approval supplement to be approved. Lastly, product that may have been recalled historically may be allowed to stay on the market at a significant savings to the industry as well as ensuring product availability to the patient.

Timeframe:

12 months to develop a step 2 document, based on a schedule of 3 ICH meetings within this time.

Risk Analysis

The main risks associated with this project are the possibility of significant disagreement between the experts who might prevent or protract the development of a harmonised guideline.

Since there are currently no national guidance documents existing in this area in any region, the risk of attachment to divergent national approaches is lower than for most ICH guidelines. In addition, it is expected that the guideline will deliver a set of principles for risk management rather than a single solution, and that this will be easier to achieve agreement on than a more prescriptive guideline.

However since there is currently no common understanding of terms, principles and application of risk management, it may take longer than anticipated to reach a common approach. To offset this, much work has been done in other industries, academia and regulatory agencies which will facilitate progress and reaching consensus.

These risks should be mitigated by oversight of the process by the Steering Committee and review against the timelines proposed.