

**White Paper**  
**In Response to the EMEA's Concept Paper**  
**Dealing with the Need for Updated GMP Guidance Concerning**  
**Dedicated Manufacturing Facilities in the Manufacture of Certain**  
**Medicinal Products**

## **Introduction**

As we stated in our original response, dated April 8, 2005, to your Concept Paper, we believe adopting a risk-based approach, such as that outlined in ICH Q9, to determine the level of control required for the safe manufacture of products, including highly hazardous substances is scientifically prudent and scientifically defensible.

In response to the growing need for guidance with respect to the manufacture of “certain” medicinal products, ISPE has formed a task team. The goal of this task team is to develop a Good Practice Guide that will outline a method by which a risk-based approach is implemented to determine the need for dedicated or segregated manufacturing facilities in the manufacture of *any* medicinal products. We invite your organization to be an active participant on this task team.

By requiring segregation or dedication as the default, least risk, strategy the regulator may have, unwittingly, a significant impact on the development, bringing to market and production of novel, life enhancing drugs. Clearer guidance at this time is crucial because of the confusion that currently exists.

This document outlines the overriding concepts that can be employed to allow a scientific risk based approach to be implemented. Once the concepts are agreed upon, details can be developed and tested to ensure compliance with the base concepts.

The application of a consistent, science based, approach will help to define if and when certain products and processes should be accommodated in dedicated or segregated facilities. The advantages of a risk based approach to aspects of quality management have been set out by ICH:-

*“Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.”<sup>1</sup>*

*“Two primary principles of quality risk management are:*

*The evaluation of risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and  
The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.”<sup>2</sup>*

An ISPE Task Team presented these views to the FDA in January 2006. The FDA was receptive to the approach and is willing to work with ISPE to develop guidance in this area. If the EMEA are interested, the Task Team would like to present our approach to you at your convenience.

## **Risk Management**

*“Although medicinal products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefits expected and the alternative available.”<sup>3</sup>*

A well-defined and consistent approach to Risk Management (Assessment, Control and Verification) is essential in defining practical and justifiable options for manufacture and sourcing of *all* products. A scientific, risk-based, case-by-case, approach should be encouraged which includes the derivation of scientifically based acceptance criteria.

A formalized **Risk Management** approach should be applied to the handling of *all* pharmaceutical compounds.

- **Risk Management** is a systematic process to identify hazards and understand risks to assist decision making to implement appropriate controls.
- The key components are hazard characterization, exposure assessment, risk characterization, control of the risks, verification of performance, communication and review.

## **Risk Assessment**

During the development of medicinal products, toxicologists, through application of rigorous scientific methods, calculate an Acceptable Daily Intake (ADI), a daily dose below which no adverse effects are expected, even if exposure occurs over the course of a life time. When developing the ADI, toxicologists can address other factors such as sensitization. The use of the ADI principle as the basis for risk assessment in the manufacture of medicinal products is a scientifically sound approach.

Decisions should not be made on the basis of **product class, definitions or labels or hazard information** alone (e.g., cytotoxic, cytostatic, steroid, potent). We need to eliminate these terms and use hazard characterization and risk characterization to describe compounds.

Compounds are potential **hazards**, and if the level of **exposure** is above the defined ADI, may present an unacceptable level of **risk**. Lowering exposure lowers risk. Provided that

there is a consistent approach to the assessment of risk then options for the control of specific risk(s) can be defined and justified.

**Hazard x Exposure = Risk.** Therefore lowering exposure to a hazard lowers risk.

- **Hazard** is the potential for a substance to produce adverse effects.
- **Exposure** is contact with the substance.
- **Risk** is the probability that a substance will produce harm under specified conditions of exposure.

It is important to note that Hazard is a “continuum” in terms of potency and severity and that exposure to any compound should be maintained below the acceptable daily intake (ADI).

**cGMP** is only one of the needs that must be met, e.g. industrial hygiene and other Health and Safety concerns must also be addressed. Solutions can vary and are sometimes conflicting. Effective **Risk Management** requires a *shared* understanding and application of assessment and control to achieve the appropriate **balance** between these different needs. It requires:

- A *multi disciplinary* approach pulling on expertise from several specialist areas, and
- A *holistic, balanced* approach.

## **Risk Control**

The controls required to manage any level of risk identified should be defined on a case-by-case basis. These should take into account the specific nature of the hazard and the exposure. These factors can be built into a science-based risk assessment process.

The risk assessment process, and the derived ADI values, should also lead to the definition of criteria to assist in the monitoring and control of risk, such as cleaning and acceptable carry-over levels.

Dedicated or segregated buildings or facilities may be required if criteria for cleaning and acceptable carryover cannot be met reproducibly. Partial dedication or segregation can offer some flexibility to a manufacturer and there are a range of potential options between total segregation and a truly multi-product facility.

Manufacturers may choose to segregate a product for purely operational reasons, (e.g., specific technology or volume). There is concern that this may sometimes be used to set precedent for products with similar hazard/risk profiles.

Risk can be controlled in a variety of ways. A combination of control measures may be required to reduce specific risks to an acceptable level. There is not a single answer. Hence a formal documented approach to risk management (such as ICH Q9) is suggested that includes the following:

- A **consistent** approach to Hazard Assessment
- A **consistent** approach to Exposure Assessment
- A **consistent** approach to Risk Assessment

This leads to the possibility of a flexible approach to how we control risk.

Operational and Quality procedures and practices should be in place, to supplement facility and equipment design, to give a high level of assurance that controls provide containment of compounds at source and prevent migration outside containment areas. In essence establishing manufacturing conditions so as to minimize the probability that a substance will produce harm (minimize risk).

Segregation or dedication should otherwise only be **required** where physical and procedural controls and/or cleaning procedures **cannot** show the ability to control potential cross-contamination to acceptable levels.

## **Operator and Product Protection**

In practice a manufacturer needs to manage the requirements of both **operator** and **product** protection. However the mechanisms of exposure and applicable exposure control strategies are very different. It is important that the risks and controls relevant to both, whilst of equal importance to a production manager, are considered separately. An over emphasis on one aspect may lead to difficulties in adequately controlling risks in the other. For example an 'over-engineered' solution to reduce risk of exposure to operators may make cleaning more difficult to achieve and lead to an elevated risk where product protection, and ultimately patient safety, is concerned. An alternative strategy that achieves a better balance, without compromising either quality or safety, may be more appropriate.

Industrial hygiene (IH) and cGMP considerations are linked because they share the same underlying toxicological data. Although an ADI will be used to derive criteria, the following are different:

- Target population: workers vs. patients.
- Typical routes of exposure: inhalation/dermal vs. oral/ IV.
- IH concerns tend to be inhalation/dermal while cross contamination is derived from airborne entrainment; mix up, mechanical transfer and retention. Airborne contamination requires the contaminant to settle into, or onto, the product or product contact surfaces; there is no direct correlation between an IH concentration data and contamination.
- Criteria for acceptability, application and interpretation.

## Cleaning

A key element of any control strategy, when considering the multi-use of a facility or process equipment, is the ability to clean consistently to a level where the risk of cross contamination of one product to another is within defined safe limits.

Arising from the Hazard and Risk Assessment processes should be criteria in support of cleaning. (e.g., swab limits based on ADIs).

Cleaning must provide a high degree of assurance that no adverse effects are expected as a result of the compound residue or related degradate levels on equipment product contact surfaces. Dedicated facilities may be required when cleaning procedures have not been shown to control the potential for cross-contamination to acceptable levels.

## Conclusion

Industry and regulatory authorities should encourage a consistent risk-based approach, as proposed, for example, in ICH Q9, to help define acceptable standards for the manufacture of medicinal products. A consistent, science-based, approach should help provide assurance that product quality will be maintained.

Segregation or dedicated facilities should only be required where physical and procedural controls **cannot** show the ability to control potential cross-contamination to acceptable levels.

The principles should be those of a consistent approach to hazard and risk assessment whilst allowing for flexibility of control strategies, recognizing that a 'one size fits all' approach is not appropriate.

Regulators might consider requesting a **documented risk management assessment** in support of the control measures put in place whether the methods are for multiple product, dedicated, or somewhere in between.

If the **Risk Management** principles are applied appropriately our experience has shown that the vast majority of pharmaceutical compounds can be handled safely in multiple product facilities.

## Future Steps

ISPE would be pleased to have the opportunity to contribute to the further review and development of GMP guidance in this area.

Separately, and in co-operation with industry and regulators, it is ISPE's intention to develop and publish guideline(s) for industry in the areas of:

1. Risk Assessment
2. Risk Management
3. Facility Design

International co-operation to achieve a harmonized approach to this important subject area is seen as being of benefit to all parties and we would welcome the EMEA's active participation in this initiative.

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<sup>1</sup> ICH Harmonised Tripartite Guideline Quality Risk Management Q9, Recommended for Adoption at Step 4 of the ICH Process on 9 November 2005 by the ICH Steering Committee

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<sup>3</sup> Report to the FDA Commissioner from the Task Force on Risk Management, May 1999