ISPE®

Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

VOLUME 7

Risk-Based Manufacture of Pharmaceutical Products

Second Edition

A Guide to Managing Risks Associated with Cross-Contamination





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Disclaimer:
This Baseline® Guide provides a scientific risk-based approach based on ICH Q9 to manage the risk of cross-contamination to maintain product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case-by-case basis to maintain an appropriate balance between assurance of product quality and worker safety. This second edition of the Guide is updated to include the new EU GMP requirements as well as additional information for cleaning, HVAC, and examples to assist the reader. This Guide is solely created and owned by ISPE. It is not a regulation, standard or regulatory guideline document. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The use of multiproduct facilities for the production of pharmaceutical products is necessary to allow products to be brought to patients in a timely and cost-effective manner. Doing this safely requires an understanding of the products, the facilities, the processes, and the equipment and the risks posed by this combination. The major risk of concern within shared facilities is the risk of cross-contamination.

New GMP guidance for the EU came into effect in 2015 that requires a risk management process to determine if products can be safely manufactured in shared facilities. This new GMP requirement left industry unsure how to perform and document these risk assessments.

This Baseline® Guide provides a scientific risk-based approach based on ICH Q9 to manage the risk of cross-contamination to maintain product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case-by-case basis to maintain an appropriate balance between assurance of product quality and worker safety. This Guide also provides examples of risk assessments and the summary report.

This second edition of the Guide is updated to include the new EU GMP requirements as well as additional information for cleaning, HVAC, and examples to assist the reader.

During the development of the first edition of this document, the FDA and EMA were actively involved and other regulatory agencies reviewed the document prior to publication. For the second edition there were discussions with the EMA to ensure that the Guide did not contradict the new GMP requirements and again other regulatory agencies, including the FDA, reviewed the document prior to publication.

Advanced Topics

Advanced Topics are noted and represent topics that require subject matter experts to address. These issues should not be addressed by those that are not familiar with the topic or do not have sufficient experience to understand how to apply the concepts appropriately.

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Subject Matter Expert Input and Review

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Acknowledgments for First Edition of this Guide

These acknowledgments are provided here as they were in the first edition at time of publication.

This Guide advocates a holistic approach to maintaining the risk of cross-contamination below acceptable limits. So it is only fitting that it was developed in this spirit by a multi-disciplinary, multi-cultural team of industry experts, which included professionals with expertise in quality systems, toxicology, manufacturing, process and containment engineering, industrial hygiene, and compliance. This Guide was a true team effort, each of the team members provided a special talent or aspect to make this project a success and they are acknowledged.

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1 Introduction

This *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products* (Risk-MaPP) provides a scientific risk-based approach based on ICH Q9 [1] to manage the risk of cross-contamination to maintain product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case by case basis to maintain an appropriate balance between assurance of product quality and worker safety.

1.1 Scope of this Guide

When considering multiproduct facilities, to satisfy regulatory requirements risk management processes are necessary to determine and document reasonable and acceptable risk. This Guide provides a process that allows manufacturers to assess risk and determine where control strategies are necessary to meet acceptable limits for cross-contamination. The control strategies to manage risk can vary from administrative to full dedication or segregation. Typically, some combination of control strategies may be necessary.

In addition, the information provided in this Guide is intended to help the user understand the relationship of hazard, exposure, and risk. If done properly, the stakeholders should be able to demonstrate a full understanding of the processes being evaluated. A consistent approach across the hazard continuum is integral in this approach so that the regulators can be confident that a well thought out plan to reduce risk to an acceptable level has been established.

This Guide is intended to provide professionals in the pharmaceutical industry with a consistent approach on setting acceptable limits to assess the potential of cross-contamination causing an undue risk to patient safety. This approach is intended to enable manufacturers to implement appropriate controls to facilitate safe and affordable drug product manufacturing without complicating the engineering solutions.

It should be noted that the use of the principles in this Guide assumes the following:

1. There is a basic understanding of the hazard spectrum of compounds and containment fundamentals
2. Subject Matter Experts (SMEs) are part of the team for the quality risk management process
3. The integrity of the data used to support the quality risk management process is of high quality and meets regulatory expectations
4. Risk management principles are not used to justify bad design or engineering practices

This Guide should be used in conjunction with local and/or applicable (multi-national manufacturing platforms) regulatory requirements and other guidance documents already available to the pharmaceutical manufacturing industry.

The principles described in this Guide can be applied equally to large and small molecular weight APIs, pre-clinical and clinical materials, and commercially marketed products in all dosage forms.

Throughout this Guide, “API” (Active Pharmaceutical Ingredient) refers to bulk drug substance and “pharmaceutical products” refers to formulated products, packaged or any intermediate bulk material or byproduct generated in the course of pharmaceutical production. This Guide also uses the term “exposure” which refers to potential patient, product, and/or operator contact with the hazard (API or product), unless specifically clarified within the text. The term “controls” as used throughout this Guide encompasses all types of controls including:

- Process controls

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- Operational controls
- The full range of engineering controls
- Procedural controls

1.2 Background

The science of toxicology recognizes the principle of a continuum of hazard associated with all compounds, even within individual classes of compounds. Zero risk is considered scientifically unachievable and not necessary. Some classes of compounds, that have historically included hormones, cytotoxic compounds, genotoxic compounds, pathogenic organisms, and veterinary products, have traditionally been placed in dedicated and segregated facilities to manage the risk. Sensitizers such as Beta-Lactam antibiotics have received particular scrutiny due to the perceived severity of potential allergic reactions. Dedicated facilities are required for manufacturing active substances and medicinal products with a high sensitizing potential for which scientific data does not support an acceptable level of exposure or the risk associated with the handling of the product at the facility cannot be adequately controlled by organizational or technical measures.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in their Q9 Quality Risk Management document [1] state: *"The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk."*

The FDA also has acknowledged this fact in the Report to the FDA Commissioner from the Task Force on Risk Management, May 1999 [2]: *"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."*

In addition, the EMEA (now known as European Medicines Agency (EMA)) acknowledged this fact in their Action Plan to Further Progress the European Risk Management Strategy, 4 May 2005 [3]: *"However, in view of the increasing and justified demands from patients and the general public for an adequate protection of public health, resulting in the availability of safe and effective medicines, it is important to re-emphasise that the concept of "zero risk" does not apply to medicinal products. The licensing of medicinal products needs to be assessed in the context of the benefit/risk balance concept, whereby demonstrated benefits must outweigh known risks, leading to a favourable benefit/risk ratio and the resulting marketing authorisation."*

When processing compounds in a multiproduct facility the risk of cross-contamination should be controlled so that products do not have any cross-contamination above established safe levels. Risk management principles are expected to be used in order to manage this risk.

1.3 Reasons for Revisions

Since the original publication of this Guide there were some significant changes in regulations and application of regulations. These include:

1. The updated EU GMPs relative to managing the risk of cross-contamination:
    a. Chapter 3 [4] was updated to allow the use of quality risk management principles to determine if products can be produced in shared facilities.
    b. Chapter 5 [5] was also updated to incorporate quality risk management principles and require toxicological assessments which refers to the EMA guideline [4] (see item 2). Chapter 5 states that the basis of controls whether technical and/or organizational should be the result of the quality risk management process.

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2. The EMA issued "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" [4] to provide guidance to industry on how to set health-based limits that would be used in the risk management process to determine if shared facilities can be used. This guideline also states "PDE and ADE are essentially synonymous".

3. ICH issued M7 "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" [7] which sets a Threshold of Toxicological Concern (TTC) for mutagenic impurities in drug substances and drug products when there is insufficient data to calculate the acceptable limit.

4. The adoption by US and EU regulators of a "life cycle" approach to process validation incorporating stages of process design, process qualification, and continued process verification. The Process Validation Life Cycle recognizes that validation is not a snapshot or an event in time, but an ongoing control strategy to manage risks and maintain process control. The concept of ongoing assurance of cleaning process efficacy is one of the keys to control of cross-contamination outlined in this guide.

5. Industry began implementing risk-based approaches to managing the risk of cross-contamination and sharing some lessons learned.

This revision of the Guide incorporates the above items and acknowledges that the overall principles presented in the original version of this Guide are still valid. To better align with the ICH Q9 [1] process some information has been relocated. Due to an increased understanding and more experience with Quality Risk Management, and more specifically with risk assessments for cross-contamination, an updated example is included in Section 14.5.

1.4 Structure of this Guide

This Guide should be read and considered holistically as reading individual subsections in isolation can lead to the unjustifiable conclusions.

The approach as outlined in this Guide is applicable to multiproduct facilities, and/or dedicated equipment, and/or dedicated areas within multiuse facilities, and is intended to offer a consistent approach, while still allowing flexibility and innovation in selecting and applying the controls necessary to manage the risk of cross-contamination to acceptable levels.

The layout of this Guide mirrors the Quality Risk Management Process as defined in ICH Q9 [1], specifically:

- Chapter 2 Concepts and Regulatory Philosophy provides a general overview of regulatory expectations and identifies key concepts presented in the Guide.

- Chapter 3 discusses the fundamentals of a Quality System (see ICH Q10 [8] for more information) and provides a methodology to logically go through the process and balance the needs of GxP and Industrial Hygiene (IH) (the "Logic Diagram").

- Chapter 4 addresses Risk Assessment, which includes the risk identification, risk analysis, and risk evaluation steps of the risk management process.

- Chapter 5 provides background and details on Risk Identification for cross-contamination, including setting health-based exposure limits.

- Chapter 6 discusses Risk Analysis and the factors that affect exposure.

- Chapter 7 focuses on Risk Evaluation where a comparison is made between the risk criteria and the identified level of risk.

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- Chapter 8 explains Risk Control strategies which include the risk reduction and risk acceptance steps of the risk management process.
- Chapter 9 Risk Reduction provides some areas to address when risk needs to be further reduced.
- Chapter 10 describes the Risk Acceptance step of the risk management process.
- Chapter 11 describes some of the risk assessment tools available.
- Chapters 12 and 13 discuss Risk Review and Risk Communication respectively as ongoing processes to make sure the risk is maintained below acceptable levels. Chapter 13 also includes a Summary Document Template for the Quality Risk Management Plan.
- The Appendices provide references, a glossary of terms, and examples of the risk assessment process described within the body of the document.

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2 Concepts and Regulatory Philosophy

The current situation is that there exists some variation between regulatory authorities in the interpretation of commensurate control strategies associated with pharmaceutical manufacturing. Worldwide, regulators are beginning to support the use of risk-based approaches to determine the acceptable level of controls required for the compliant manufacture of highly hazardous compounds (i.e., those compounds that can cause serious adverse effects at low doses) within multiproduct facilities, but there are still several regions that have not embraced a risk-based approach. The US FDA and the EMA are expecting a documented risk assessment to determine if products can be produced in shared facilities as well as helping to identify the controls necessary to manage the risk of cross-contamination in these shared facilities. Several other major regulatory agencies allow for the production of highly hazardous compounds by campaign, provided adequate separation and suitably validated cleaning procedures are present, while other regulatory bodies do not allow certain highly hazardous compounds in multiproduct facilities at all.

2.1 EudraLex – European Commission GMP Updates

In August of 2014 the European Commission updated Chapters 3 and 5 to provide improved guidance on managing the risk of cross-contamination. These changes encourage the use of risk management principles to manage the risk of cross-contamination. Both chapters reference a toxicological evaluation as described in the EMA "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" [6].

Section 3.6 has updated guidance on when dedicated facilities are required:

> *"Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:*
>
> *i. the risk cannot be adequately controlled by operational and/or technical measures,*
> *ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or*
> *iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method."*

Sections 5.17 to 5.22 provide more detail on the expectations to manage the risk of cross-contamination. These sections state that the design of processes, equipment, and facilities are important in managing the risk of cross-contamination and that a Quality Risk Management process, including a toxicological evaluation, is to be used to assess and control the risk of cross-contamination. The process should determine if dedicated equipment and/or facilities are necessary, as well as any technical or organizational control measures. The need to periodically monitor the controls in place to manage the risk of cross-contamination is also stated.

Specifically, Section 5.20 states *"A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family."*

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2.2 EMA Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities

The EMA introduced this guideline [6] in November 2014. This guideline introduces the Permitted Daily Exposure (PDE) to determine a substance specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. This is an extension of the PDE introduced in ICH Q3C(R6) [9] for residual solvents. This guideline outlines the process used to develop a substance specific PDE and a suggested summary document. The EMA document also states that the PDE and ADE are essentially synonymous. This guidance document is applicable to API manufacture as well as finished dosage manufacture.

2.3 EudraLex – European Commission GMP Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use

Annex 2 [10] states *"Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and medicinal products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination."*

2.4 EudraLex – European Commission GMP Annex 15: Qualification and Validation

The cleaning validation section of Annex 15 [11] (as well as other sections) was updated in 2015. The Annex states that *"Limits for the carryover of product residues should be based on a toxicological evaluation."* and the EMA guideline [6] on setting health-based exposure limits is referenced. PIC/s Annex 15 [12] adopted the same language in a recent update.

2.5 US FDA 21 CFR 211.42

The US FDA regulation that often is cited when there are concerns with cross-contamination is 21 CFR 211.42 [13] that states *"There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination..."* for all classes of compounds.

During the planning meetings for the original ISPE Risk-MaPP Baseline® Guide published in 2010 [14], the FDA specifically requested that this Guide:

- Provide an approach to identify highly hazardous drugs
- Provide a risk management/assessment model that gives a clear view on how to address the controls to comply with 21 CFR 211.42(c) [13]
- Discuss how the approach fits into cleaning validation

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2.5.1 Approach to Identify Highly Hazardous Drugs

The original intention of this Guide was to provide a method to identify highly hazardous compounds. However, during the development of the first edition, it became apparent that an approach to identify acceptable risk in the manufacture of pharmaceutical products was more appropriate. Criteria are provided in Chapter 5 (Risk Identification) to help identify the most hazardous drugs.

In order to identify acceptable risk, it is necessary to first assess and categorize a compound. Using information such as toxicological data about a hazard or specific population risk, will help mitigate emotive, hazard-based decision making. Terms such as "potent", "cytotoxic", "cytostatic", and "steroid" are not precise when categorizing specific API hazard potential, and conclusions based on a reactive response, rather than specific scientific data, should be avoided.

Health-based limits should be developed by toxicologists from available toxicological and pharmacological data from preclinical studies, data from clinical trials and other information typically submitted, as required, with Marketing Applications (i.e., New Drug Applications (NDAs), Biological License Applications (BLAs), or Marketing Authorization Applications (MAAs)) normally in Common Technical Document (CTD) format.

This Guide refers to this health-based limit as the Acceptable Daily Exposure (ADE) value. The ADE value represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime. By definition, a robust ADE limit is intended to be protective of all subpopulations and by all routes of administration. The ADE can be considered synonymous with the PDE (EMA, 2014 [6]). Establishment of the ADE value is an important first step in a risk assessment and the inherent assumptions should be consistent with how it is applied within the product mix in a given facility. The author of the ADE monograph should be consulted if there are questions about how it should be applied within the risk assessment.

This Guide is predicated on some key concepts and definitions:

"Hazard" is the inherent property of a compound to produce harm. If a hazard is present, then a risk exists because of the potential for exposure.

"Exposure" is contact with the hazard. The exposure is dependent on the control systems used when handling the hazard as well as the form of the hazard and how often and in what quantities the hazard is handled.

"Risk" is the probability of occurrence of harm at a given level of exposure, and also reflects the severity of that harm (i.e., consequences of failure). Care should be taken with the use of subjective assessments (qualitative) and the assignment of risk scores. Wherever possible appropriate data should be used to assess the risks. If data are not available, a plan to obtain data may be necessary.

Since the hazard (including its severity) cannot be changed, the primary way to control risk to the patient via cross-contamination of the product, or health risks to the worker, is to control the level of exposure to the hazard.

2.5.2 Risk Management/Assessment Model to Address the Controls to Comply with 21 CFR 211.42(c)

21 CFR 211.42(c) [13] states that *"Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such **other control systems** for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures: …"*

It should be noted that other regulatory bodies such as the EMA, the World Health Organization (WHO), and the Ministry of Health, Labour and Welfare (MHLW) have similar requirements. In addition, the US FDA Center for Biologics Evaluation and Research (CBER) [15] allows the manufacture of live vaccines in multiproduct facilities, provided adequate controls are established to prevent cross-contamination. This Guide can assist vaccine manufacturers in determining and documenting that adequate control is provided to maintain the risk of cross-contamination below acceptable levels.

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To determine the control systems that meet the intent of the US FDA CFR, risk assessments should be undertaken, starting with the development of the health-based acceptance criteria (e.g., ADE, cleaning validation limits, etc.). These provide the basis for a risk analysis, which includes exposure assessments to provide a risk profile. Each manufacturer should determine if the risk is acceptable without establishing further control strategies to manage the risk. If the risk is above acceptable levels, then further risk reduction strategies should be employed. In terms of cross-contamination it is understood that the risk should be consistently controlled within the ADE/PDE. See Section 9 for further information on risk reduction.

The risk management approach should be continued throughout the life cycle of the product. This type of risk-based approach provides and documents an understanding of the products being processed, the processes being used, and the way the equipment and facility will be cleaned to support both patient and worker safety. Risk management measures should include safe handling of materials, to minimize the potential for cross-contamination and to protect workers from unacceptable exposures. When this is accomplished, manufacturers should be able to make products with a degree of flexibility in the manufacturing process, while maintaining both patient and worker safety.

2.5.3 How the Approach Fits into Cleaning Validation

Residues from a compound which remain after cleaning on equipment or other product contact surfaces may pose a risk to patient safety. A scientifically-based risk assessment of such compounds should be performed, in order to understand the impact of this risk.

Cleaning procedures should be developed to minimize the risk from residues. To reduce risk, cleaning procedures should be capable of reducing residues to, or below, a predetermined safe level based on the risk assessment for a compound, as well as to ensure that the equipment is totally visibly clean.

An appropriate cleaning agent should be identified for each compound. A scientifically-based risk assessment should be performed on the cleaning agent, which should pose the least risk to patient safety.

A risk analysis of the cleaning procedure should be performed, using the information obtained from the initial risk assessment of a compound, to determine the acceptability of the cleaning procedure.

2.5.4 Regulatory Environment

The pharmaceutical industry and its regulation continue to evolve. In the 1990s, the ICH was formed to promote joint international harmonization of regulatory requirements between industry and regulators for the manufacture and development of pharmaceutical products. In the early 2000s, regulatory agencies began encouraging manufacturers to improve their processes to increase both safety and efficiency.

From 2003 through 2015, ICH working groups produced several significant documents; ICH Q3C(R6) and Q3D, Q7A, Q8(R2), Q9, Q10, Q11, Q12 and ICH M7 [16]. These documents have been or are being adopted by the ICH parties (US, Japan, and EU) and used worldwide by industry to harmonize these issues.

ICH Q3C(R6) [9] introduced the Permitted Daily Exposure (PDE) concept to be used for residual solvents in drug products. EMA furthered the concept of the PDE to identify safe exposure limits for pharmaceutical compounds in the guideline they issued in November 2014 [6].

ICH Q3D [17] provides clarification for determining the limits (PDEs) for elemental impurities in drug products and ingredients.

ICH Q7 [18] section IV.D (4.4) on containment states *"Dedicated production areas…..should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins. The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved … unless validated inactivation and/or cleaning procedures are established and maintained."*

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ICH Q7A Q&A [19] was published in 2015 and clarified ICH's position on the use of quality risk management processes to determine the need for dedicated API facilities and the containment measures expected to control the risk of cross-contamination.

> *"ICH Q7 expects dedicated production areas for highly sensitizing materials such as penicillins and cephalosporins because of the patient risk (e.g. anaphylactic shock to penicillin-allergic patients) from trace amounts of these compounds in other medicines* [ICH Q7, Section 4.40].
>
> *For materials of an infectious nature or high pharmacological activity or toxicity, a risk-based approach should be used to determine appropriate containment measures, which may include validated inactivation, cleaning and/or dedicated production areas* [ICH Q7, Section 4.41]"

ICH Q8(R2) [20] introduced Quality by Design which is based on the *"concept that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks."*

ICH Q10 [8] discusses the importance of an effective pharmaceutical quality system throughout the product life cycle, and responsibility of senior managers to create a quality policy that assures compliance with applicable regulatory requirements and facilitates continual improvement.

ICH Q11 [21] provides *"further clarification on the principles and concepts described in ICH Guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of drug substance."*

ICH Q12 [22] provides *"guidance on a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle."*

ICH M7 [7] provides recommendations for assessment and control of mutagenic impurities and sets a limit of 1 in 100,000 excess cancer risk for mutagenic impurities.

In 2002, the FDA announced its Pharmaceutical cGMPS for the 21st Century – A Risk-Based Approach [23] initiative which was *"intended to modernize FDA's regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines."* In 2007, the FDA changed the name of the initiative to Pharmaceutical Quality for the 21st Century – A Risk-Based Approach "to capture the larger issue of product quality, with cGMPs being an important tool towards improving overall product quality." [24]

The goals outlined in the FDA's Pharmaceutical Quality for the 21st Century – A Risk-Based Approach [24] support:

- New technological advances by the pharmaceutical industry
- Modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Risk-based approaches that focus both industry and Agency attention on critical areas
- Regulatory review, compliance, and inspection policies are based on state of the art pharmaceutical science

In 2005, Dr. Janet Woodcock, Chair, Council on Pharmaceutical Quality, FDA provided a view on the desired state of the pharmaceutical industry as *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."* [25] This is still quoted by the FDA as a desired state.

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In early 2008, Center for Biologics Evaluation and Research (CBER) revised 21 CFR 600.11(e)(4) [15]:

> *"The revisions provide that live vaccine processing steps may be performed in multiproduct manufacturing buildings and areas when appropriate controls exist to prevent cross contamination of other products and areas. We recognize that advances in facility, utility, system, and equipment design, as well as in sterilization, decontamination, and disinfection technologies have increased the ability of manufacturers to control the manufacture of biological products and the equipment used in their manufacture. The use of appropriate controls, procedures, and processes provides an adequate degree of confidence that a product meets the expected levels of safety, purity, and potency. Areas of special concern, such as containment, decontamination, sterilization, and disinfection can be addressed using currently available controls, procedures, and processes."*

The 2011 FDA Process Validation Guideline [26] states that it is based on the basic principle that a drug should be produced that is fit for its intended use, and goes on to say that this principle incorporates the understanding that:

1. Quality, safety, and efficacy are designed or built into the product

2. Quality cannot be adequately assured merely by inspection or testing

3. Each step of a process must be controlled to assure product meets all quality attributes

In the context of this Guide, "quality product" is defined as the absence of unacceptable adulteration due to cross-contamination with other products produced in a shared facility. In the terminology of ICH Q8(R2) [20], lack of adulteration can be said to be a Critical Quality Attribute (CQA) for **all** pharmaceutical products. As with all other CQAs, there must be risk control strategies to assure that each batch conforms to quality specifications. These controls must be specified, designed, qualified (validated), and maintained in an ongoing and continued manner. Ongoing process control requires an understanding of the sources and impacts of process variability. The FDA guidance recommends that manufacturers:

1. Understand the sources of variation

2. Detect the presence and degree of variation

3. Understand the impact of variation on the process and ultimately on product attributes

4. Control the variation in a manner commensurate with the risk it represents to the process and product

In 2015 the FDA CDER created the Office of Pharmaceutical Quality (OPQ) to provide "One Quality Voice" which will allow a uniform approach to quality for all drug products serving the US market including generic and over the counter drugs. The following are the OPQ's objectives:

1. Assure that all human drugs meet the same quality standards to safeguard clinical performance

2. Enhance science and risk-based regulatory approaches

3. Transform product quality oversight from a qualitative to a quantitative and expertise-based assessment

4. Provide seamless integration of review, inspection, surveillance, policy, and research across the product life cycle

5. Encourage development and adoption of emerging pharmaceutical technology

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These concepts apply to many aspects of pharmaceutical manufacturing. Applying these concepts to manage the risk of cross-contamination, introduces the following additional key concepts:

1. Risk is a function of hazard and exposure. Any compound should be considered a hazard. The severity of this hazard will depend on the type of effect that can be caused, and on the dose at which this effect will appear. Exposure is the level of contact with the compound. Risk is the likelihood that a compound will produce harm under specified conditions of exposure. To minimize risk, manufacturing conditions and procedures should be established to control exposure, thus minimizing the probability that a compound will produce adverse effects.

2. Like criticality, there is a continuum of hazard: there are no distinct lines at which to distinguish certain compounds as low hazard from others that are high hazard. See Figure 5.2.

3. Pharmacological and toxicological descriptions (e.g., dose response, critical effect, Point-of-Departure (PoD), No-Observed-Adverse-Effect Level (NOAEL), and ADE) should be used to assess the hazards of compounds. Subjective terms such as potent, cytotoxic, cytostatic, and other product class definitions tend to induce an emotional response that may imply that, without exception, these compounds are always difficult to handle and require the highest level of control.

4. A consistent, robust, and science risk-based approach in decision making should be made across the hazard continuum.

5. Organizations should ensure a well-supported estimation of risk, a strong scientific rationale for risk acceptance, and a robust design approach. Care should be taken with the use of subjective assessments (qualitative) and the assignment of risk scores. Wherever possible appropriate data should be used to assess the risks. If data are not available, a plan to obtain data may be necessary.

6. Health-based exposure limits, such as ADE values, should be used as a basis when calculating limits for the determination of acceptable risk. These limits represent the boundaries of toxicological safety and while they may be supplemented with additional criteria (e.g., visually clean) , they should not be artificially reduced to provide “safer limits”. Such arbitrary limit setting is not scientifically justifiable and sets up scenarios where a non-conformance to approved criteria may be “signed off” as acceptable on the rationale that the stated limit was tighter than necessary anyway. The preferred approach is to understand how well the process performs and set alarm and alert limits that are below the acceptable risk limits. By incorporating alarm and alert limits an organization can have better control over the processes without breaching acceptance criteria.

7. Exposure, and subsequently risk, can be reduced to acceptable levels by a variety of methods (this includes strictly excluding the presence of certain compounds within the facility).

8. GxP is the primary focus; however, IH (worker safety) and other health and safety concerns also should be addressed. Solutions can vary and are sometimes conflicting. Effective risk management requires a shared understanding and a holistic application of assessment and control to acceptable levels, to achieve the appropriate balance between these different needs (this includes strictly excluding the presence of certain compounds by design).

9. Plausible pathways for exposure to the hazard, whether for patient, product, or worker need to be correctly understood and addressed.

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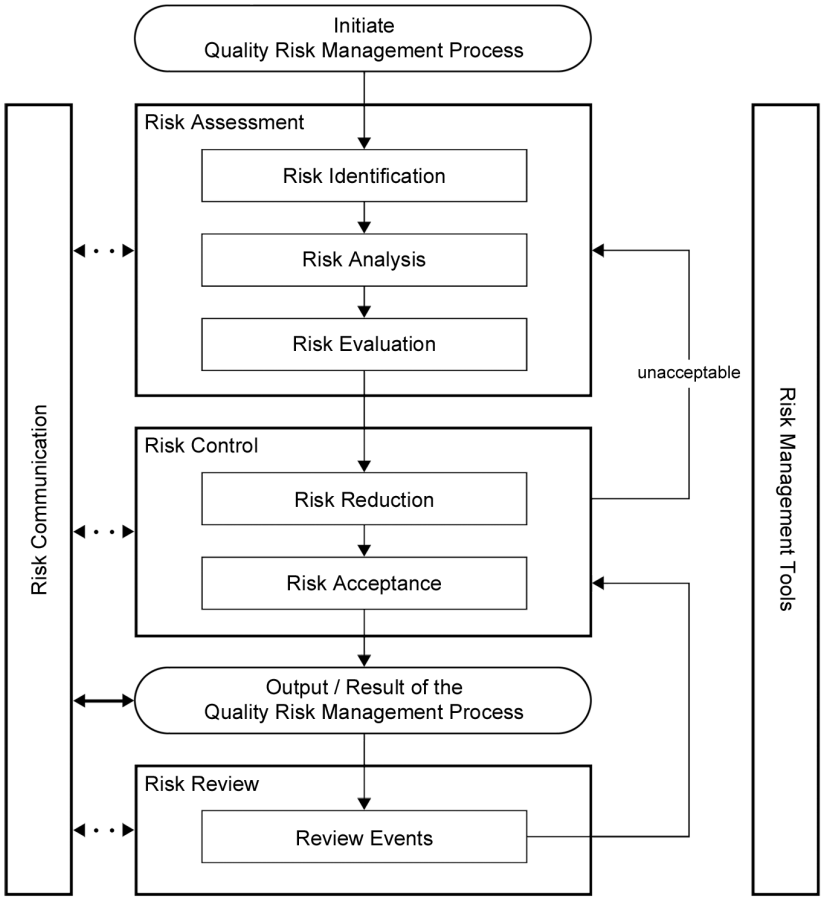
2.6 Overview of the Risk Management Approach

A risk management approach should be applied to the handling of pharmaceutical products. This should be a holistically defined process to formally identify hazards and understand risks to assist decision making for the implementation of appropriate approaches for risk control. Although this process should be a formal part of an organization's quality system, the level of effort and detail for the risk management process can, and should, vary based on the perceived risks which are based on hazard, including severity and probability of occurrence.

The risk assessment process should be used to derive criteria that can assist in decision making and control strategies to manage the risks to the patient. The risk assessment should be a transparent evaluation of all data relevant to hazard identification, assessment of potency (dose response) and severity, exposure assessment, and characterization of risk. The risk assessment should be documented and should include a discussion of all assumptions and limitations inherent to the risk assessment performed. Risk control strategies that are implemented should be commensurate with the level of risk which is based on hazard, including severity and probability of occurrence. The ultimate decision on the appropriate control strategy implemented may rely on both qualitative and quantitative data.

ICH Q9 [1] outlines a quality risk management process that is iterative and consists of the identification of the hazards and the analysis and evaluation of risks associated with exposure to those hazards, as well as control strategies to manage the risks. This Guide follows the steps outlined in ICH Q9 and customizes them to address cross-contamination risks.

Figure 2.1: ICH Q9 Quality Risk Management Process



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2.7 Use of Health-Based Exposure Limits

An API represents a hazard, as it is capable of producing biological effects (e.g., pharmacological or toxicological). The likelihood that these effects will occur depends on:

- The dose-response relationship
- The amount absorbed as determined by the route, level, and duration of exposure

The ADE takes these into consideration and reflects a safe dose which incorporates a margin of safety. The risk of exceeding the ADE as a cross-contaminant in another product depends on how well potential contamination can be consistently controlled.

The main premise of this Guide is that if exposure to an API is kept below a prespecified level that is determined to be safe, this would indicate low risk for adverse health effects in exposed individuals. At this level of exposure, the risk of experiencing any effects is extremely low and is considered acceptable.

Regulatory agencies and expert committees use a similar hazard assessment process to establish safe levels of exposure to substances that include chemicals in the workplace and the environment, food additives, and impurities in pharmaceutical products. A number of different terms have been used to describe the health-based limits developed for different purposes. For example, for many years Acceptable Daily Intake (ADI) values have been established for indirect food additives. Tolerable Intake (TI) values have been developed for similar purposes. The ICH has recommended Permitted Daily Exposure (PDE) values for residual solvents and elemental impurities in pharmaceutical products and the EMA has further developed the PDE concept for use in determining safe levels of pharmaceutical compounds. More recently, the ICH has finalized ICH M7 [7] on setting limits for genotoxic impurities in pharmaceutical products. The US Environmental Protection Agency (EPA) [27] establishes Reference Doses (RfDs) and Reference Concentrations (RfCs) to regulate air and water emissions. Examples of Occupational Exposure Limits (OELs) include: Occupational Safety and Health Administration (OSHA) [28] Permissible Exposure Limits (PELs), American Conference of Governmental Industrial Hygienists (ACGIH®) [29] Threshold Limit Values (TLV®s), German AGW (Arbeitsplatzgrenzwert (Workplace Limit Value)) and MAK (Maximale Arbeitsplatz-Konzentration (Maximum Workplace Concentration)) values [30], and the European Commission Scientific Committee on Occupational Exposure Limits (EC SCOEL) Indicative Occupational Exposure Limit Values (IOELVs) [31].

The health endpoint of concern, and the subpopulation being protected, will influence what level of risk is acceptable. For example, the ACGIH® TLV® Committee recommends that exposures to irritants be maintained just below a level that can cause irritation in workers. Exposures are allowed to approach this level, as this effect is a mild and reversible one. For target organ effects and other non-cancer endpoints, adjustment factors (also called safety factors, uncertainty factors, and assessment factors) are used by limit setting groups worldwide. These are applied to the No-Observed-Adverse-Effect Level (NOAEL) for the critical endpoint (the first significant effect observed at the low end of the dose-response curve) to derive a safe level of exposure. The critical effect for patients may be different than that for operators due to differences in the route(s) of exposure. This often represents the first clinically significant pharmacological effect. The actual risk cannot be easily quantified, but no unwanted effects are expected at or below this dose, i.e., there is a margin of safety reflected by the ADE value. The lower the exposure is below the limit, the larger the margin of safety.

A different approach has been used for carcinogens that are based on risk. OSHA has promulgated PELs for carcinogenic substances to maintain cancer risks, generally in the range of 1 in 1,000. The US EPA [27] and California EPA (Proposition 65) [32] regulate carcinogens to 1 in 100,000 excess cancer risk in the general population while the ICH M7 [7] uses 1 in 100,000 excess cancer risk for mutagenic impurities.

In order to determine the level of acceptable risk, a number of factors need to be balanced by the benefits associated with a product. These benefits are different for patients and workers.

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2.8 The GMP and Industrial Hygiene Balance

A clear strategy is necessary to assess risk in either the Industrial Hygiene (IH) or cGMP setting and to define scientifically based criteria in order to make decisions for managing risk. Although criteria for both are derived from the same toxicological or clinical data, the way in which these data are used to derive acceptable limits and adequate control strategies will differ. It is important to understand these differences and the possible consequences of confusing the two.

The key differences relate to the application and interpretation of target population, routes of exposure, and acceptability criteria. These are summarized in the Table 2.1.

Table 2.1: Summary of Differences for IH and cGMP Considerations

Perspective	Industrial Hygiene	Quality (cGMP)
WHO/WHAT Exposed Population Variables (Age, Immunology, Fitness)	**Worker** Usually healthy	**Product** Introducing risk to Patient via the product
Route of Entry	**Inhalation** Dermal Transmucosal Membranes Ingestion	**Product Cross-Contamination** by settled powder or retained product X into/onto Product Y
Primary Exposure Mechanism(s) or how exposure/cross-contamination occurs	**Inhalation** (settled dust can be resuspended to be breathed at another time) **Skin Absorption** contact, via wounds **Mucous Membranes** contaminated worker touches mucous membranes **Ingestion**	**Mix-Up** wrong materials **Retention** inadequate cleaning **Mechanical Transfer** moving residue from one thing to another **Airborne Transfer** powder available in air and contacts product, equipment
Basis of Standards for Risk Assessment	**Occupational Exposure Limit (OEL)** expressed by an airborne concentration (mass per cubic meter of air) to address primary route of entry for exposure: Inhalation **Wipe Limit** expressed as a surface concentration (mass per square centimeter) to address dermal exposure	**Acceptable Daily Exposure (ADE) Value** expressed as mg/day **Cleaning Limit** expressed as mg/swab or mg/l to address primary route of exposure, e.g., Ingestion, IV

Balancing the needs of both IH and GMP interests is very important in ensuring that all risks, to product or worker, are adequately managed. Only through recognizing the differing needs and identifying a strategy that can address both is it possible to achieve safe, efficient, and economic operation of a manufacturing facility.

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3 Quality System Requirements

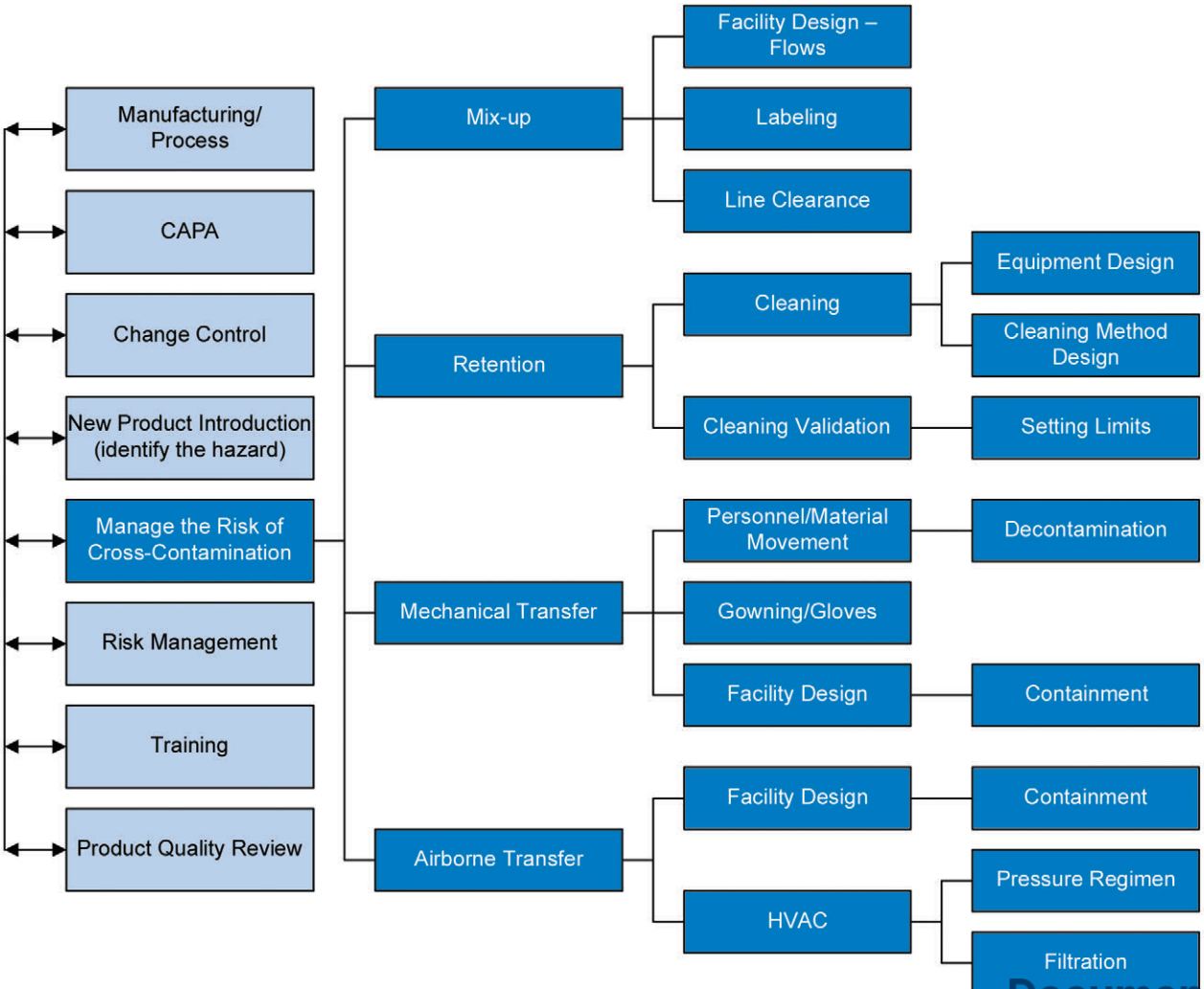
A well-defined quality system should consist of governance documents which are complemented by a concise set of tactical or procedural requirements. The overarching documentation matrix should provide the basis of consistency required for the creation of a sustainable quality system model which enables the ICH Q10 [8] life cycle approach across the GxP regulated functions within an organization.

3.1 Application to Cross-Contamination

The key concepts discussed in this Guide should be used as a framework from which to develop standards, tools, and approaches to manage the risk of cross-contamination.

A case by case assessment should be performed of the risk factors that the concurrent manufacture of several products may cause. Risk assessments should be performed to properly understand the implications for both IH and GxP. While each is normally considered separately, to prevent any significant imbalance, the implications of decisions taken during an assessment for IH should be checked against those for GxP, and vice versa.

Figure 3.1: Quality Management System



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3.1.1 Suggested Quality Policies/Standards for Managing the Risk of Cross-Contamination

While many aspects for managing the risk of cross-contamination are covered in various quality documents such as cleaning and cleaning validation, line clearance, etc., it is suggested that overarching quality policies, standards and SOPs are put in place to manage the risk of cross-contamination that tie together these various aspects.

Other quality systems that are impacted or related to managing the risk of cross-contamination include:

1. Technology Transfer (New Product Introduction)

   Firms should have a well-documented procedure for assessing potential products prior to introducing them into the facility. This should include:

   a. A mechanism that triggers an assessment of the potential cross-contamination risks prior to bringing the product/compound into the facility. The outcome of this assessment is to determine if the product (the hazard) can be adequately controlled in a shared facility and/or what level of dedicated equipment and/or facility may be required.
   b. The hazards of the product(s) should be identified typically via an ADE monograph.
   c. Cleaning process development prior to introducing the product into the facility. In situations where this is not possible, a robust risk assessment that considers all available historical information and cleaning performance data to assess the risk from the cleaning process, should be performed. Verification of the cleaning should also be performed after each campaign of the new product introduced when cleaning development activities are not able to be completed.
   d. Analytical methods sensitive enough to meet the required acceptance criteria

2. Risk Management

   The Risk Management quality system should provide a common understanding of risk and how to assess it. Senior management should provide guidance on how to determine acceptable and unacceptable risk. It is suggested that this be established at the corporate level so that there is a common understanding across the organization that helps to facilitate sharing of information and comparison of different facilities.

3. Change Control

   It is suggested that the change control process includes a trigger for risk review when the change may impact the risk of cross-contamination. Such changes may include new product introduction, the ADE value of product, maximum daily dose for products, equipment changes, facility changes including changes to HVAC or water quality/pressure, process changes (e.g., scale, formulation, etc.), or procedure changes.

4. Corrective and Preventative Action (CAPA)

   An outcome of the risk assessment activities may be to implement some risk reduction controls. The CAPA system may be used to track the risk mitigation measures until implemented and confirmation of performance is complete.

5. Product Quality Review

   Results from the risk management process may become part of the product quality review as appropriate. In addition, requalification or monitoring programs should also provide an indication that the risk of cross-contamination is in a controlled state.

6. Training

   It is important that basic GMP training for all relevant staff includes practices that are designed to avoid cross-contamination as well as understand how cross-contamination occurs. Staff involved in managing the risk of cross-contamination should have further training in both how to avoid cross-contamination and quality risk management.

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3.2 The Logic Diagram

A logic diagram is a simple tool that can be used to guide a team through a process to determine the adequacy of existing controls or the need for dedicated facilities. (Section 3.6.1 should be read in conjunction with the flow diagram in Chapter 14.) Determining the need for dedicated facilities should be performed by a multidisciplinary team, so that all required areas are addressed appropriately.

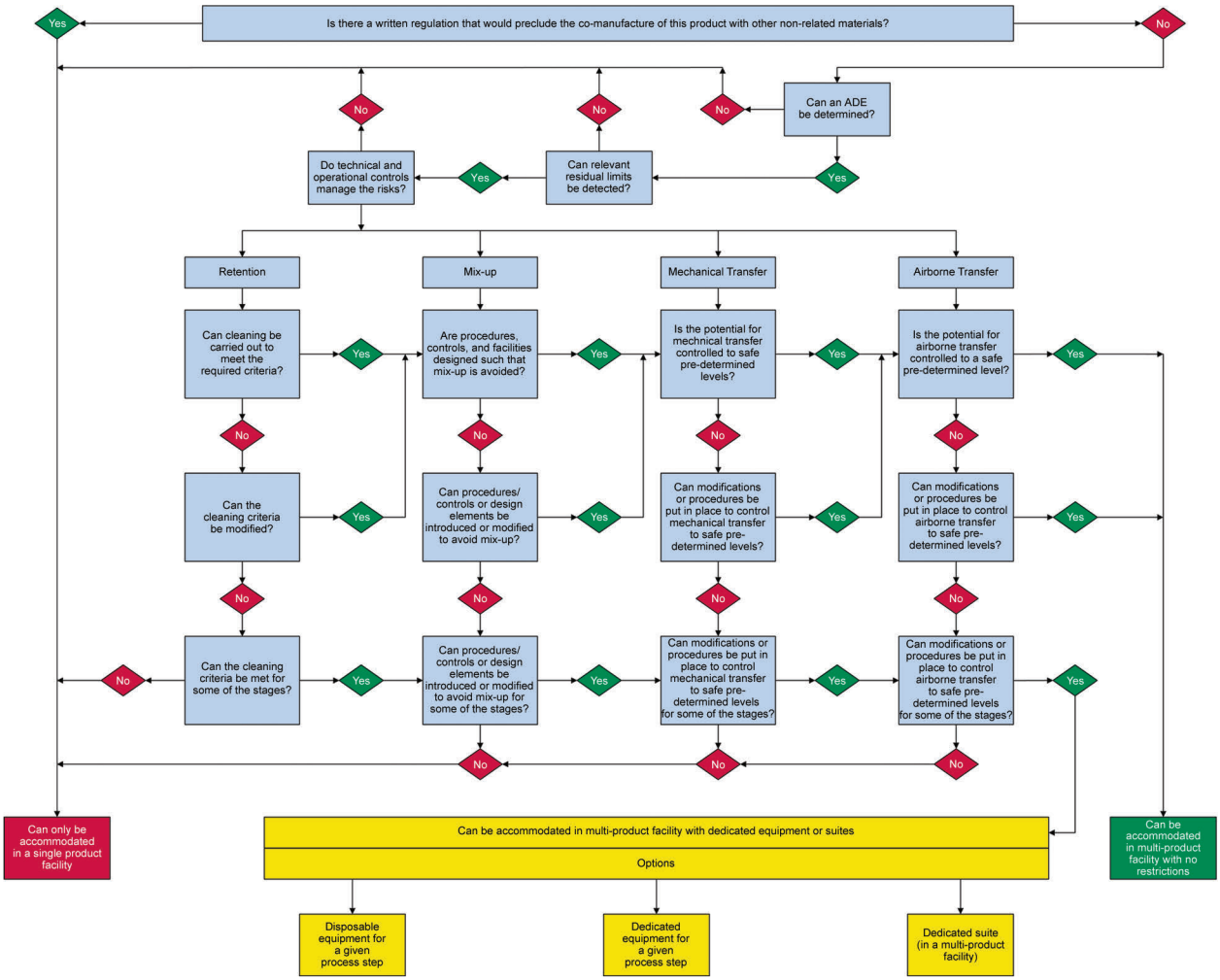
The logic diagram is divided into two, addressing both GMP/Regulatory logic and IH logic. Both are equally important as they deal with aspects of risk associated with the different populations that may be exposed to the hazard under review (left side – product, right side – worker).

Where dedicated facilities are implemented for business reasons, the risk assessment should clearly state that this is a business decision and not a cross-contamination issue.

3.2.1 Considering the GMP/Regulatory Factors

See Figure 3.2. For a larger version of the diagram, see Chapter 14.

Figure 3.2: GMP/Regulatory Factors



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3.2.1.1 Gathering Hazard Information (e.g., Health Based Criteria)

Both the IH and GMP criteria are drawn from common toxicological or clinical data sources. Each should have a science-based approach to risk management and clear strategies for the assessment of potential exposure, (e.g., monitoring). The ADE value is normally the health-based criterion used in assessing GMP concerns related to cross-contamination. The OEL is normally the health-based criterion used in assessing airborne product for worker protection.

3.2.1.2 Specific Requirements for Handling Product in a Dedicated Facility

"Is there a written regulation that would preclude the co-manufacture of this product with other non-related materials?"

This is the first question of the logic process.

The usual example quoted is that of the beta-lactam class of antibiotics where some current GMPs, e.g., 21 CFR 211.42(c)(d) [13] **require** separate facilities for their manufacture, processing, and packing. The updated EU EudraLex Vol. 4 Section 3.6 [4] requires dedicated facilities if:

1. *"the risk cannot be adequately controlled by operational and/or technical measures"*
2. *"scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitizing materials such as beta lactams)"*
3. *"relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method."*

These issues are not necessarily understood at this point in the logic diagram. It is expected that by following the logic diagram these aspects will be understood.

In addition to the criteria above that reflect the hazard and likelihood and severity of harm there are numerous reasons to dedicate a single product to a single facility, including:

- A consequence of a product specific agency inspection
- Internal QA recommendation
- Manufacturing technology may be unique to the product
- Sales demand may be sufficiently high to fully utilize available capacity

Operational reasons for dedicated facilities should not be used to set a precedent for similar materials in different settings; this should be determined on a case by case basis.

It may not be possible to reduce the degree of risk to an acceptable level without incurring time or cost penalties. In this case, the pragmatic approach may be to dedicate a facility. The situation should be revisited if key factors change (manufacturing or containment technology improves, demand changes, etc.).

3.2.1.3 Determining an ADE

"Can an ADE be determined?"

Based on the information from the Gather Hazard Information it will be known if the scientific data from the toxicological evaluation supports the determination of an ADE. See Chapter 5 for more information.

If the information supports the determination, then an ADE value should be determined and passed on to the other stakeholders for further assessments by following the logic diagram.

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If the information does not support the determination of an ADE value, then a dedicated facility is required. As noted above, this is where the beta-lactam family of products would be addressed.

3.2.1.4 Detection of Residue Limits

"Can relevant residue limits be detected?"

Proper utilization of equipment requires knowledge of the potential for retention or carryover from one product to another. This is a characteristic based on the chemical and physical nature of the compound and the design and materials of construction of the equipment. The acceptable level of retention or carryover should be determined, on a case by case basis, taking into account the hazard(s) presented by the product and the nature and route of administration of the product that will next be processed in the equipment, suite, or facility. An appropriate safety margin should be incorporated when establishing acceptable levels. See Chapters 5 and 6 for further information.

Compounds that can be denatured/degraded/deactivated require studies to ensure the effectiveness of the process to render the residues as safe. The basis for this study should include development of an ADE value to assess the margin of safety of the remaining residues that could potentially carryover to the next product's production.

Once the relevant cleaning residue limits are known, validated analytical methods should be established in order to detect that the cleaning residue limits have been met.

If residue limits for other purposes are used (e.g., for air monitoring), validated analytical methods may also be required.

If analytical methods cannot be validated to the appropriate level, then a dedicated facility is necessary.

3.2.1.5 Technical and Operational Controls

"Do technical and operational controls manage the risk?"

Each of the modes of cross-contamination should be assessed to determine whether technical and operational controls can manage the risk.

Care should be taken when assessing manual operations and the controls in place to detect manual errors. A strategy to reduce the risk of manual errors is required.

3.2.1.6 Cleaning (Retention) Aspects

"Can cleaning be carried out to meet the required criteria?"

Factors to be considered when assessing whether the cleaning criteria can be met or detected, include:

- Feasibility: if a very low level of acceptable carryover is defined, are there analytical methods that will achieve the level of detection required? If an aggressive cleaning agent (e.g., caustics or acids) will be used, what effects will this cleaning agent have on the equipment or materials of construction? Will there be pitting or corrosion of surfaces with long-term use? Will equipment parts become corroded or damaged over time (e.g., gasket materials)? The risk assessment should consider such possibilities.

- Practicability: is the cleaning method consistent and easy to complete (automated versus manual)? For manual cleaning are the procedures detailed sufficiently for consistent cleaning regardless of the variability of the personnel? Would the effort required to perform cleaning to the defined level be practical? Would the facility need to be shut down for an extended period? Would extra personnel be required to undertake the cleaning? Would high volumes of solvent or other chemicals be required presenting a different risk scenario (e.g., exposure of workers to the cleaning materials, containment and cost of disposal of solvents)?

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- Cost: are the direct and indirect costs associated with an extended clean down acceptable? If this is a once a year scenario the answer may be "yes." However, if this is an exercise that may need to be conducted weekly, it may not be an economically feasible option.

- Patient: the above considerations do not supersede the needs of the patient who ultimately will be administered or consume the drug product. It is important to note that risk to the patient is one of the primary focuses of the risk assessment.

If these factors can all be addressed satisfactorily, then the use of a multiproduct facility with shared equipment may be a viable option for the processing or manufacture of the material or product under consideration. If the answer is no or not easily to any of the above questions, then some element of dedication should be considered.

A number of additional questions should be addressed before confirming the feasibility of a multiproduct facility. The logic diagram poses further questions, which should be answered on a case by case basis to determine the degree of dedication that may be required.

3.2.1.7 Cleaning/Retention Resolution

"Can the cleaning criteria be modified?"

For example, if the current method cannot be validated to the appropriate sensitivity, consideration to improving the method is an option.

If the cleaning criteria are hard to achieve, improving or altering the cleaning procedure and/or cleaning agents is an option.

If a worst-case approach is used, and the new product to be introduced is a new worst case and is difficult to achieve, excluding the new compound from the worst case and treating it as a separate condition may be an option.

3.2.1.8 Partial Cleaning/Retention Resolution

"Can the cleaning criteria be met for some of the stages?"

If these factors cannot be addressed easily, dedication may need to be considered. Total dedication of an entire facility or equipment train may be unnecessary. Instead, dedicating or using single use technology for some of the equipment train, to help make the cleaning residue criteria more manageable, may be a cost-effective option.

3.2.1.9 Mix-Up Aspects

"Are procedures, controls, and facilities designed such that mix-up is avoided?"

Factors to be considered when assessing whether mix-up can be avoided include:

- Procedures/SOPs: identify areas where the existing procedures may fail or the consequences if the procedures are not followed. Are additional procedures needed? Are the existing procedures too complicated to follow? Are the procedures verified by suitable means?

- Controls: identify areas where the existing controls may fail. Are additional controls needed?

- Facility Design: is the facility layout such that there are no shared process flows or areas of process overlap? If not, can the procedures and controls effectively prevent mix-up?

If these factors can all be addressed satisfactorily, then the use of a multiproduct facility may be a viable option for the processing or manufacture of the material or product under consideration. If the answer is no or not easily to any of the above questions, then some element of dedication should be considered. See Chapter 6 for further information.

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3.2.1.10 Mix-up Resolution

"Can procedures/controls or design elements be introduced or modified to avoid mix-up?"

It may be necessary to conduct a number of specific, low level, assessments in order to be confident that any risks associated with the accommodation and processing of the material under consideration can be managed or reduced to an acceptable level. In this situation, it should be possible to use a multiproduct facility.

3.2.1.11 Partial Mix-up Resolution

"Can procedures/controls or design elements be introduced or modified to avoid mix-up for some of the stages?"

If these factors cannot be addressed easily, dedication may need to be considered. Total dedication of an entire facility may be unnecessary, however, even if achievable without incurring a significant extra cost. Instead, a more limited approach to segregation or dedication may be a cost-effective option.

3.2.1.12 Mechanical Transfer

"Is the potential for mechanical transfer to be controlled to safe predetermined levels?"

Factors to be considered when assessing whether the mechanical transfer criteria can be met include:

- Process: is the process closed? Can material escape the process and be transported around the facility via equipment, product, intermediates, supplies, and personnel moving through the facility?

- Procedures: are procedures and/or controls in place to minimize mechanical transfer, e.g., gown changes prior to leaving processing rooms? Are procedures and/or controls in place that states equipment is to be wiped down prior to leaving the processing rooms? Are there means to prevent transfer from feet or wheels?

- Facility: are there other GxP issues that might introduce risk? For example, would movement of personnel or materials within the facility or inadequate differential pressures between manufacturing zones give cause for concern? A more specific risk assessment to review these aspects may be warranted.

- Operational Standards: is the facility being operated to a standard that is adequate for the processing of the materials under consideration? Is specialist knowledge required? Do process and maintenance workers need specialist training prior to handling the product? Is containment managed through engineering controls alone or are additional procedural controls used? Are these adequate? If there is a reliance on engineering controls does this introduce issues at changeover from one product to another? Such questions may be particularly relevant if considering the use of a third-party Contract Manufacturing Organization (CMO).

If these factors can all be addressed satisfactorily, then the use of a multiproduct facility may be a viable option for the processing or manufacture of the material or product under consideration. If the answer is no or not easily to any of the above questions, then appropriate dedication strategies should be considered. See Chapter 9 for further information.

3.2.1.13 Mechanical Transfer Resolution

"Can modifications or procedures be put in place to control mechanical transfer to safe predetermined levels?"

It may be necessary to conduct a number of specific, low level assessments in order to be confident that any risks associated with the accommodation and processing of the material under consideration can be managed or reduced to an acceptable level. In this situation, it should be possible to use a multiproduct facility.

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3.2.1.14 Partial Mechanical Transfer Resolution

"Can modifications or procedures be put into place to control mechanical transfer to safe predetermined levels for some of the stages?"

If these factors cannot be addressed easily, dedication may need to be considered. Total dedication of an entire facility may be unnecessary; however, even if achievable without incurring a significant extra cost. Instead, a more limited approach to segregation or dedication may be a cost-effective option.

3.2.1.15 Airborne Transfer

"Is the potential for airborne transfer to be controlled to safe predetermined levels?"

Factors to be considered when assessing whether the airborne transfer criteria can be met include:

- Process: is the product exposed to the room environment during processing, transfer, or cleaning? Is the process closed? Can material escape the process?

- Facility: are there other GxP issues that might introduce risk? For example, would movement of personnel or materials within the facility or inadequate differential pressures between manufacturing zones give cause for concern? Are material and personnel airlocks provided? If so, are they adequate at controlling airborne transfer? A more specific risk assessment to review these aspects may be warranted.

If these factors can all be addressed satisfactorily, then the use of a multiproduct facility may be a viable option for the processing or manufacture of the material or product under consideration. If the answer is no or not easily to any of the above questions, then some element of dedication should be considered. See Chapter 9 for further information.

3.2.1.16 Airborne Transfer Resolution

"Can modifications or procedures be put into place to control airborne transfer to safe predetermined levels?"

It may be necessary to conduct a number of specific, low level assessments in order to be confident that any risks associated with the accommodation and processing of the material under consideration can be managed or reduced to an acceptable level. In this situation, it should be possible to use a multiproduct facility.

3.2.1.17 Partial Airborne Transfer Resolution

"Can modifications or procedures be put into place to control airborne transfer to safe predetermined levels for some of the stages?"

If these factors cannot be addressed easily, dedication may need to be considered. Total dedication of an entire facility may be unnecessary; however, even if achievable without incurring a significant extra cost. Instead, a more limited approach to segregation or dedication may be a cost-effective option.

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3.2.1.18 Accommodating Product in a Multiproduct Facility

"Can the product be accommodated in a multiproduct facility, but with more specific dedication?"

When dealing with highly hazardous materials, application of a thorough risk management approach to a specific accommodation or manufacturing proposal, may allow the need for total dedication to be reasonably challenged. However, the risk assessment(s) may not provide sufficient confidence to allow co-manufacture with all other products currently being handled within the same facility. In such cases, it is worth considering some limited dedication or segregation to address those aspects of the handling or process seen as still posing an unacceptable level of risk:

- Dedicated Suite/Room in a multiproduct facility: dedicating a defined suite, room, or area may be sufficient to address local risks associated with cleaning and/or other GxP concerns unique to the materials and processes under consideration.

- Dedicated Equipment: dedication of an individual vessel or item of processing equipment, or contact parts (e.g., feed chutes, compression tooling, and filling heads) may be all that is required to reduce the specific area of risk under review. Consideration should be given to the cleaning, storage, and segregation of such items.

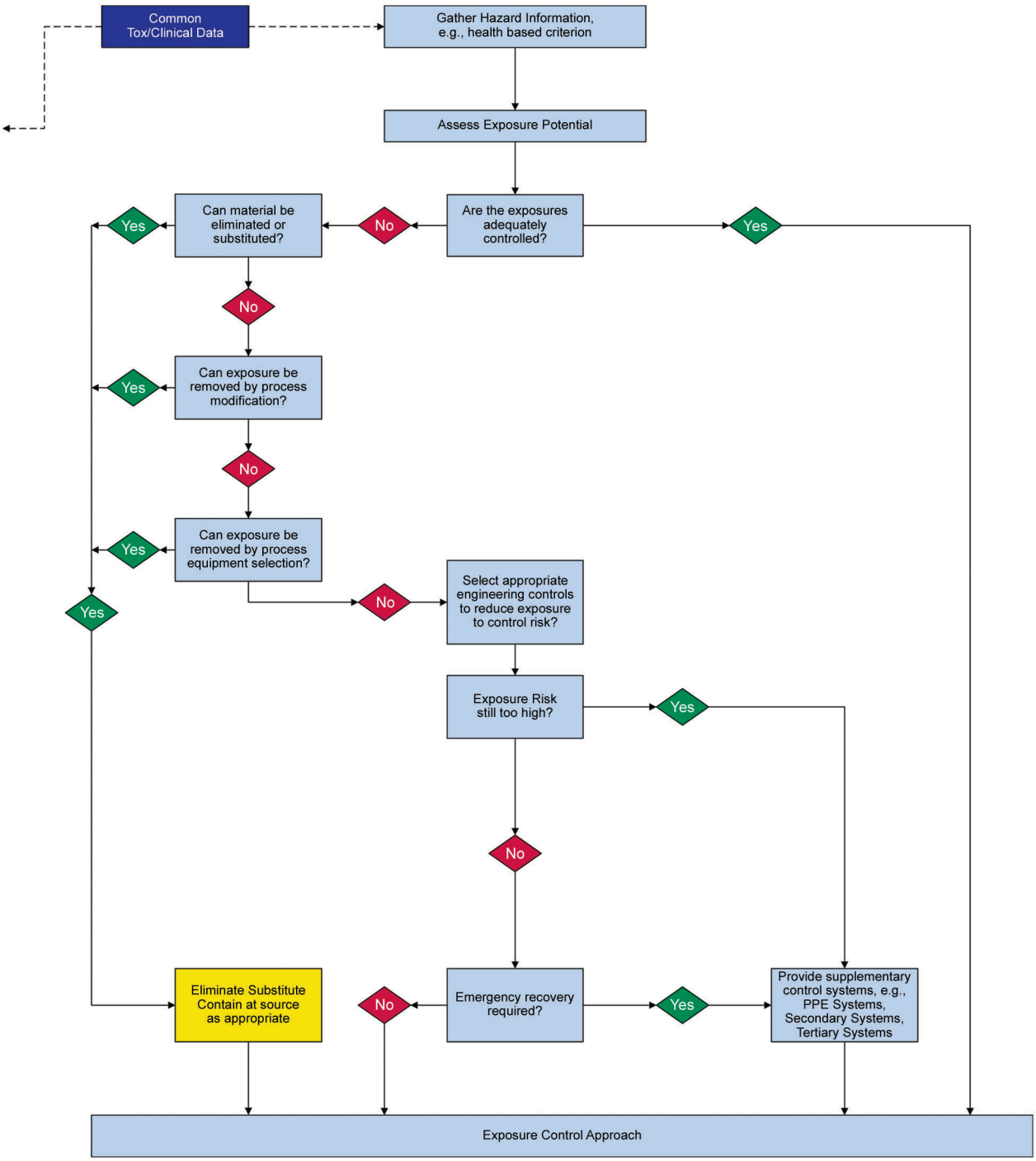
- Disposable Equipment: it may be more economical to dispose of and replace small items of equipment (e.g., filling tubing, filters, or glassware), an option which is being utilized increasingly in the biotechnology sector. In this situation, it is still necessary to consider the cleaning/decontamination requirements and the consequences of disposal. How will the items be transported and disposed of? This should be the subject of a further, specific risk assessment.

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3.2.2 Considering the Health and Hygiene Factors (Applicable to Personnel)

See Figure 3.3. A larger version of the diagram is provided in Chapter 14.

Figure 3.3: Health and Hygiene Factors



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3.2.2.1 Gather Hazard Information (e.g., Health-Based Criteria)

Both the IH and GMP criteria are drawn from common toxicological or clinical data sources. Each should have a science-based approach to risk management and clear strategies for assessment of potential exposure, (e.g., monitoring). The OEL is normally the health-based criterion used in assessing airborne levels of API from bulk or finished product for protection of workers.

3.2.2.2 Assess Exposure Potential

Exposure potential may differ depending on the way a material is processed or the facility where processing occurs.

Risk is a function of both hazard and exposure. Evaluating the likelihood of exposure is a key part of the risk management process. Several factors should be considered:

- Who is at risk of exposure? – Workers at the line, maintenance personnel, general personnel in the area, or QA personnel when sampling product?
- What factors might influence exposure? – Is it a dusty powder? Is it a liquid? Is it a closed or open process? How well trained are the personnel? Is it a routine or frequent task?
- What is the pathway for exposure? – Inhalation, ingestion, or skin absorption?
- When is exposure most likely to occur? – Do workers need to directly intervene in the process for sampling, at process breakdown, clean down, or product changeover?

3.2.2.3 Control of Exposure

"Are the exposures adequately controlled?"

Information that is already available should be reviewed to help determine how well exposure is controlled:

- Is there experience with the material under review? – Have any adverse health effects been reported? Does the nature of the material (e.g., wet, lumpy, solid) or the process (e.g., closed) suggest that risk is unlikely to be high?
- Are there any hard data? – Are there any monitoring data available? Are there similar or identical processes being operated in other facilities?
- What is known about the exposure profile for the specific product and process as it is operated, or might be operated, in a particular facility?

The controls that are applied should be commensurate with the risk and should be considered in the context of all the requirements of the manufacturing process, e.g., whether a particular engineering control would make it difficult to intervene if the process runs out of control or makes it very difficult to clean without affecting efficient plant utilization.

3.2.2.4 Process Changes

"Is elimination, substitution, or process change possible?"

While process or formulation changes are often difficult to make with established products, the opportunity to reduce exposure potential by this means is feasible if considered early enough in the product development process. Examples where this has been shown to be effective include:

1. Removal of a solid recovery step between stages in a chemical process

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2. Change to a wet granulation process from a direct blend process for tablet manufacture

3. Addition of a film coat to a tablet in order to reduce the risk of exposure during packing

4. Formulate as a liquid/semisolid in a capsule rather than as a conventional tablet or powder filled capsule

Each of these examples addresses only one step in a process chain and potential for exposure may still exist in other steps.

3.2.2.5 Selection of Engineering Controls

Once risk factors have been investigated, control measures can be considered. The correct control system should be determined and should consider such factors as cost, feasibility, ergonomics, ease of cleaning, and failure mode operation, i.e., what to do if the control measure fails.

Thought needs to be given about converting the knowledge on exposure potential into the performance requirements for engineering controls. How much confidence can be placed on Assigned Protection Factors (APFs)? What experience is there in-house of using similar control options?

3.2.2.6 Level of Exposure Risk

"Is the exposure risk still too high?"

Having selected a control to address a measured exposure, what happens if the exposure risk is still at an unacceptable level? Is it reasonable to add in a secondary system, such as an extract system, to reduce the exposure potential to an acceptable level?

Is routine use of Personal Protective Equipment (PPE) acceptable for an activity of short duration? There is no clear answer and such options should be discussed with operating personnel, plant management, and HSE specialists. In some cases, operators may prefer PPE if a more permanent rigid barrier makes the process step difficult to perform from an ergonomic perspective.

3.2.2.7 Emergency Recovery

"Is emergency recovery required?"

What happens if the primary containment system fails? What knowledge is there of the possible failure modes and their frequency for a given system? Is failure acceptable under any circumstances? Such factors should be considered as part of the risk assessment.

- What will need to be recovered, how, and by whom?
- What supporting infrastructure will be required? For example:
  - Would PPE need to be provided?
  - Would change areas, showers, storage areas for PPE be required?
  - Would a separate air supply be required to service any PPE?

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3.2.2.8 Secondary PPE

"Is secondary control or PPE required?"

Where available, the rationale for the use of secondary PPE should be well understood and documented. Is it provided to supplement a primary control measure and reduce an assessed exposure potential to an acceptable level? Is it provided for emergency use only?

3.2.3 Consequences of Control Strategy

The consequences of adopting any particular exposure control strategy should be rechecked against the GxP/ regulatory logic to ensure plant operability is not comprised.

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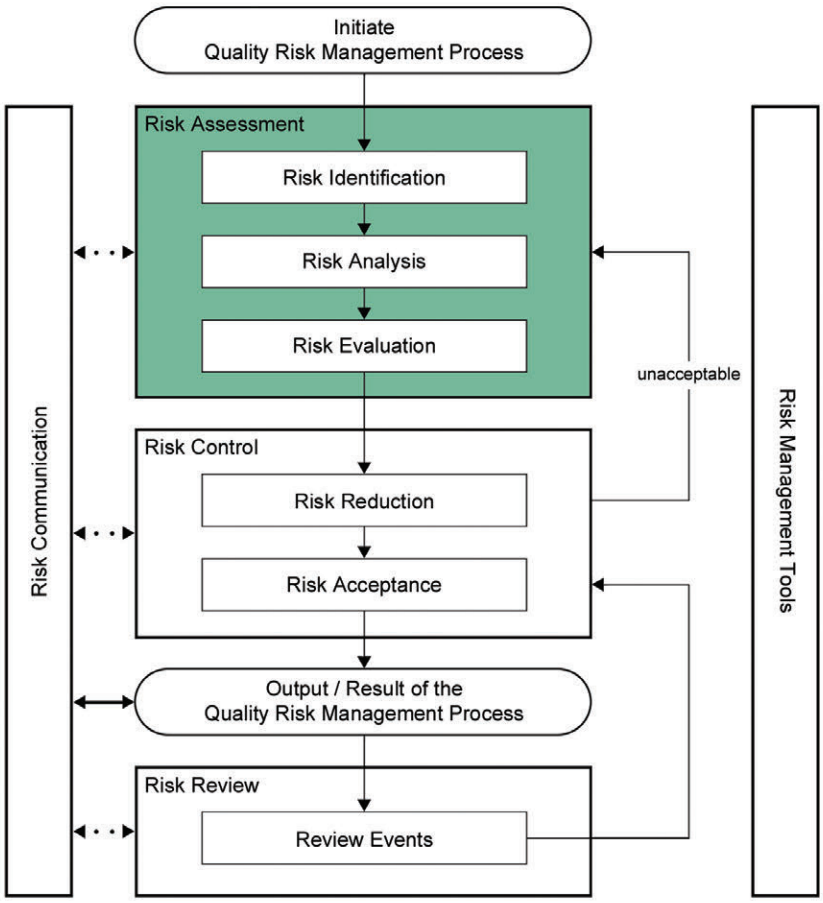
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4 Risk Assessment

Risk assessment as described in ICH Q9 [1] encompasses three steps: risk identification, risk analysis, and risk evaluation. Each of the three steps helps to answer the three fundamental questions:

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the consequences (severity)?

Figure 4.1: Risk Assessment



The risk assessment steps may be considered the most important aspects of an overall quality risk management process. If the risks are not identified, analyzed, and evaluated properly, the decisions on how to control the risk cannot be made adequately.

The criteria for judging acceptability of risk for cross-contamination and operator exposures differ, although GxP and IH considerations are linked because they share the same underlying toxicological data as the starting point from which they are both derived. In addition, the application and interpretation of the criteria in the risk assessment process will be different.

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Part of the risk assessment process is to consider if there are realistically any plausible pathways that might give rise to an increased risk of exposure. For example, when considering airborne transfer, the following risk questions should be asked:

- Can cross-contamination from an airborne pathway occur? Specifically, can product A be directly distributed via the air stream or resuspended back into the air (after being deposited) in a room/suite/facility, and then settle or get redeposited directly into product B or onto contact parts to be used for the manufacture of product B?

- Can this occur in sufficient amount that the ADE for product A might be exceeded should a patient be administered the now contaminated product B?

- Is it plausible for product that has been deposited on equipment or adjacent work surfaces to be redispersed into the air stream and present an exposure risk for operators via inhalation?

Similar questions should be asked to understand the risks associated with mix-up, retention, and mechanical transfer.

Consideration of plausible pathways should be on a case by case basis as part of the overall risk assessment. These pathways, typically, are different for patients and operators.

At the conclusion of the risk assessment, risk should be expressed in quantitative or qualitative terms depending on the data available from the three steps of the risk assessment.

This information should then be used in the decision making to accept or reduce the risks under the risk control steps.

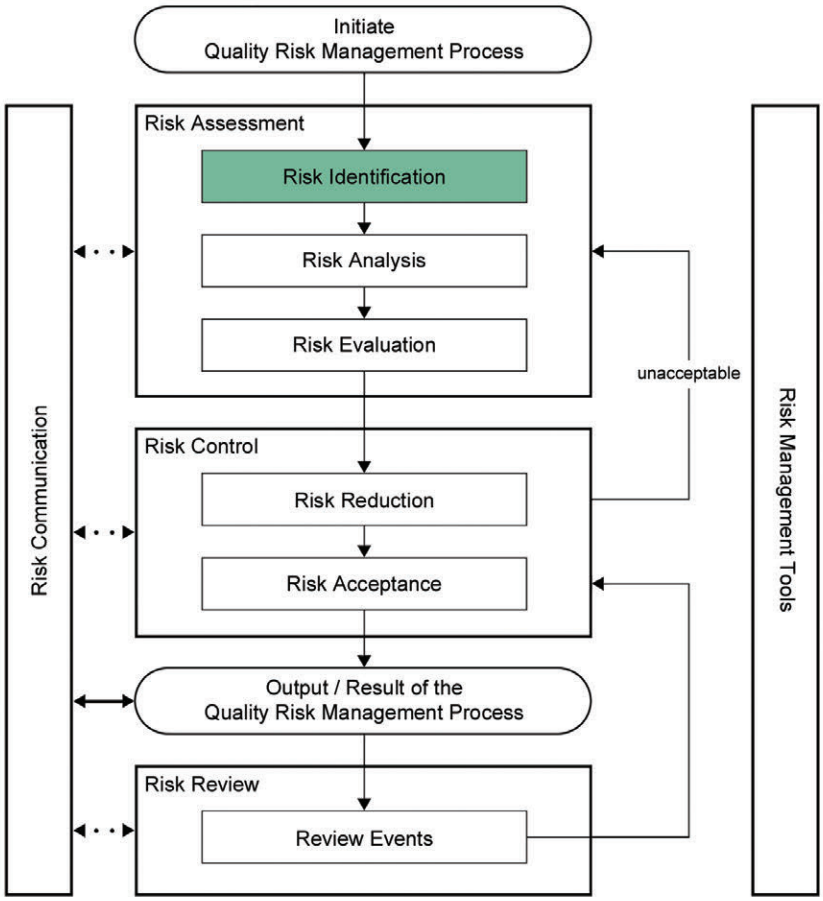
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5 Risk Identification

This Chapter describes risk identification, which starts with qualitative hazard identification, i.e., the process by which existing hazards are identified, initially without assigning magnitude. All available animal and human data should be reviewed to address the question: "What could go wrong?" This first step in the risk assessment process also includes identifying possible consequences. It serves as a prelude to later steps of risk analysis and risk evaluation that ultimately lead to appropriate exposure control and management of risk.

Figure 5.1: Risk Identification



5.1 Definition of Hazard

Hazard is defined in ICH Q9 [1] as a potential source of harm. ICH Q9 also includes the severity of harm in the definition of risk. Within the context of this Guide, hazard describes the inherent property of a compound to produce adverse effects, e.g., in patients that may be exposed to the compound as a trace contaminant in another pharmaceutical product. The compounds typically considered include:

- APIs
- Process intermediates
- Solvents

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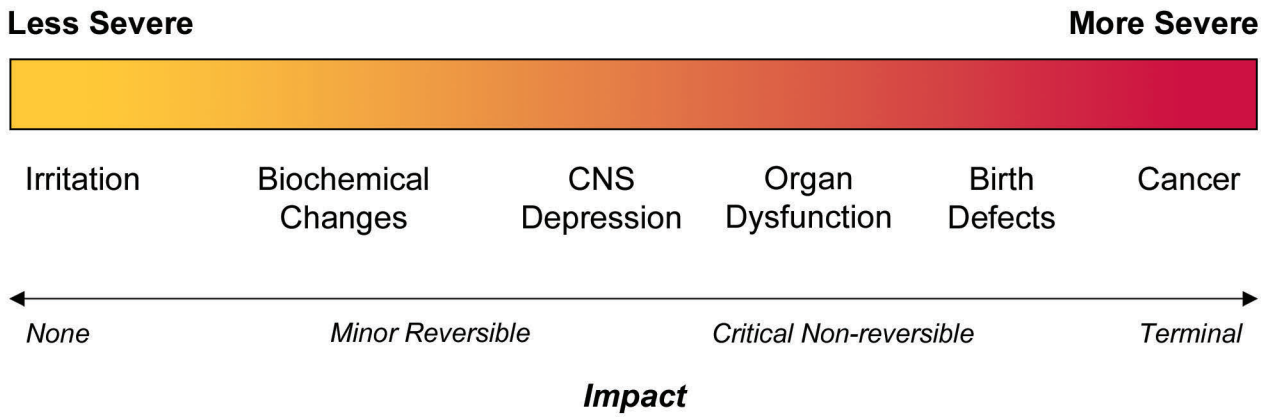
- Excipients

Other compounds that may need to be considered include impurities, byproducts, and degradants. Each compound has its own inherent ability to cause adverse effects (i.e., toxicity) – effects that may be well documented in the case of the API, but may be unknown for other compounds.

5.2 Hazard Continuum and Prioritization for Risk Assessment

Depending on the hazardous properties of an individual compound (see Figure 5.2), resulting from its mechanism-of-action and potency, health-based limits, such as the ADE values, can span several orders of magnitude. It is preferable to derive these health-based values for all pharmaceutical compounds, regardless of potency, to ensure the protection of patients. Similarly, there is a need to focus attention on those compounds with the lowest health-based exposure limits because these may be the compounds that are the most difficult to control, and the consequences of overexposure may be the greatest. In general, special controls may be needed to maintain exposures to these compounds below acceptable levels. As part of an overall risk management approach, it is useful to have a qualitative tool to help determine the need for, and to prioritize, comprehensive quantitative risk assessments. This tool should ideally incorporate the severity of the effect/impact on quality of life, reversibility of the effect and likelihood of death.

Figure 5.2: Hazard Continuum



One approach is to apply a set of criteria to identify the most hazardous drugs in a health care facility. Some pharmaceutical organizations have developed criteria to identify compounds in the same or similar categories highlighted in various GxP guidance documents, i.e., *"certain steroids, certain antibiotics, certain cytotoxics, and other highly active compounds."* [33] Other pharmaceutical organizations use a control banding approach to categorize compounds into categories of increasing severity based on their inherent pharmacological and toxicological properties. Sussman et al. (2016a) [34] provide guidance on how to identify and assess highly hazardous drugs within a quality management system.

The following criteria can be used to identify highly hazardous drugs and should be used as just one input of a comprehensive risk assessment/risk management program. Identification of a compound as a hazardous drug should not automatically lead to strict control solutions (e.g., a dedicated facility) because it addresses only hazard although, because of potential risks to operators, these compounds tend to have more control than low hazard drugs. A risk analysis, as described in Chapter 6, should be completed before any conclusions can be made about risk and the need to modify controls.

Criteria for identifying hazardous drugs and prioritizing risk assessments include:

1. Genotoxic compounds that are known to be or highly likely to be carcinogenic to humans

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2. Compounds that can produce reproductive and/or developmental effects at low dosages*

3. Compounds that can produce serious target organ toxicity or other significant adverse effects at low dosages*

*For example clinical doses < 1 to 10 mg/day or animal doses < 0.1 to 1 mg/kg/day

The use of Occupational Exposure Limits (OELs) and Occupational Exposure Bands (OEBs) can be used to estimate ADE values for the purpose of prioritization in risk assessments, which also includes an assessment of potential exposure. Use of OELs and OEBs has the advantage of capturing concerns for potency, severity and reversibility of effect, and alteration of the quality of life and length of life. Extrapolating an OEL to an ADE value, in its simplest sense, is accomplished by multiplying the OEL (µg/m^3) by 10 m^3, the volume of air breathed by a worker in 8 hours (ADE (µg/day) = OEL (µg/m^3 × 10 m^3). The simple estimation of an ADE using an existing OEL is meant only to facilitate risk ranking. This does not mean a formal ADE should not be derived if an OEL exists. If an OEL has been established, it means that sufficient data were available to derive a numerical value. The same data can be used to derive a formal ADE and this activity should be routinely performed and documented to support formal risk assessments as part of a quality risk management program.

Many companies assign new compounds to an OEB, or equivalent designation corresponding to airborne concentration ranges, to provide guidance on safe handling before sufficient data are available to establish a numerical OEL. The OEB is assigned based on the compounds' inherent pharmacological and toxicological characteristics, including the intended use, mechanism of action, dose-response, and data from available studies. One option is to use the OEBs to estimate ADE values for the most hazardous subset of compounds (i.e., those with the most restrictive OEBs). Estimating ADE values from OEBs involves using the same approach used for OELs, as applied to the lower end of the range of airborne concentrations associated with the OEB (see example in Table 5.1). There are some limitations regarding the use of OELs and OEBs to estimate ADE values due to potential differences in the target subpopulation(s), critical effects, and differences in bioavailability. For this reason, a qualified toxicologist should be involved in these estimations.

Table 5.1: Estimating ADE Values Using Occupational Exposure Bands (OEBs) – An Example

OEB	Concentration Range	Low End of the Band	Estimated ADE*
1	≥ 1 < 5 mg/m^3	1 mg/m^3	10 mg/day
2	≥ 0.1 < 1 mg/m^3	0.1 mg/m^3	1 mg/day
3	≥ 10 < 100 µg/m^3	10 µg/m^3	100 µg/day
4	≥ 1 < 10 µg/m^3	1 µg/m^3	10 µg/day
5	< 1 µg/m^3	< 1 µg/m^3	< 1 µg/day
* Estimated ADE = Low End of the Band × 10 m^3			

The approaches described in this Guide for estimating ADE values using OELs and OEBs for purposes of prioritizing risk assessments, may also be useful early in drug development before sufficient data are available to set formal ADE values, e.g., when GMP material is being manufactured for initial clinical trials. In all cases, these approaches should be considered an interim strategy until formal, fully documented ADE values can be developed.

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5.3 Establishing Health-Based Exposure Limits

The foundation of a risk-based approach for manufacturing pharmaceutical products comprises:

- The identification of hazards
- Assessment of dose-response relationships
- Establishment of health-based limits

The identification of hazards and assessment of dose-response relationships are collectively referred to as hazard characterization.

Having an understanding of how a compound can cause harm, and at what dose, is crucial to evaluating risks and deciding on appropriate exposure controls.

In addition to identifying what could go wrong, this step in the risk assessment process also provides important information on the consequences of exposure. Such consequences are considered in the establishment of a health-based limit (e.g., ADE) taking both the dose-response relationship and the severity of effect into account.

The approach used to derive ADE values is consistent with a number of guidance documents on setting health-based exposure limits that are available (e.g., WHO 2005 [35]).

Industry toxicologists also have published a number of peer reviewed articles on setting health-based exposure limits (Sargent and Kirk, 1988 [36]; Conine et al., 1992 [37]; Galer et al., 1992 [38]; Naumann and Weideman, 1995 39]; Schwartz, 1995 [40]; Silverman et al., 1999 [41]).

More recently, several reviews have been published summarizing these earlier publications and incorporating, and building on, the information on setting health-based exposure limits provided in the first edition of this Baseline® Guide (Sargent, et al., 2013 [42]; Bercu et al., 2013a [43]; Sussman et al., 2016b [44]). The EMA guidance document on setting Permitted Daily Exposure limits (PDEs) based on the ICH Q3C(R6) [9] guidance for residual solvents utilizes a similar set of adjustment (assessment) factors. As mentioned above, the PDE is essentially synonymous with the ADE. Where applicable, similarities and differences, albeit minor, will be identified below.

The guidance provided in this Chapter reflects the general principles and selected specific recommendations from these guidance documents and peer reviewed articles. It also describes the basic elements of a toxicological evaluation, as this term is used in the EMA guidance on setting health-based exposure limits and the EU GMPs (Vol. 4, Chapters 3 and 5 [4, 5]). In practice, the methods used to derive health-based exposure limits may differ slightly, but it is the responsibility of the organization to ensure that all relevant sources of uncertainty and variability are addressed, regardless of which adjustment factor covers them, and that their recommended limits are scientifically defensible and adequately protective.

5.3.1 Data Collection and Analysis

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For hazard identification, a formal review of all available relevant animal and human data should be performed for each compound. This review should be done by a qualified toxicologist. This is an individual that has many years of experience setting health-based limits such as ADE values and OELs, preferably in the pharmaceutical industry. Specific training in toxicology is necessary, whether at MS or PhD level, but degrees in related fields such as pharmacology or medicine may be sufficient when coupled with appropriate specific training and experience. Certification in general toxicology is desirable but not required.

For the innovator companies that developed the API, the data used in the analysis should include the data submitted in the regulatory filing. Contract Manufacturing Organizations (CMOs) should request this information, and the rationale for the ADE that may have already been derived, from the innovator company asking them to manufacture the drug

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The reviewer should have access to the full range of preclinical and clinical data required for approval of the drug. For non-proprietary compounds, all relevant information on the potential hazards of the material should be obtained through reliable sources. Standard toxicology and pharmacology reference texts should be consulted and a literature search (e.g., on PubMed[1]) should be performed. The internet is also a useful source for information on generic drugs provided trusted sources are used. Searching on the generic name of the drug often surfaces much of the information needed to derive a health-based exposure limit. Drug approval agencies (e.g., FDA, EMA, National Competent Authorities) are good sources for summary documents on APIs and associated marketed products. Caution should be used when utilizing Safety Data Sheets (SDSs) as a reference source, since the credibility of the information may vary. The toxicologist performing the hazard assessment and calculating the health-based exposure limit is responsible for assessing the gathered data from the publicly available sources with regard to relevancy, adequacy, and reliability of the collected information. The hazard characterization process should commence once all of the relevant information has been compiled.

5.3.2 *Identification of the Critical Effect*

The purpose of a hazard evaluation is to identify all possible hazards associated with a compound and to rank them according to their severity. When combined with a dose-response assessment, the critical effect can be defined. This is typically the first clinically significant adverse effect that is observed as the dose increases.

The critical effect should be used for the derivation of an ADE. Ideally, the critical effect should be derived from studies for the same route that the ADE value will be used to evaluate. Extrapolation from data for other routes may be necessary if relevant route specific data are not available. Exposures below the No-Observed-Adverse-Effect-Level (NOAEL) for the critical effect should not, by definition, lead to other effects, as these will only occur at higher doses. The reviewing toxicologist should determine which of the effects reported at low dosages is the critical effect. It may be necessary to evaluate several endpoints, which may involve different sets of adjustment factors. A justification should be made considering the final ADE value, which is based on the most sensitive effect relevant to humans. The same approach for evaluating animal data is used for risk assessments involving veterinary products.

Due to differences in the route of exposure, the toxicological profile of the compound in question and the potential for local effects at the site of contact, the critical effect may be different for patients and operators.

Professional judgment is required to discern between biological effects that may be physiological or adaptive changes or subclinical pharmacological effects of the drug, which would have associated Lowest-Observed-Effect Levels (LOELs). These biological effects should be distinguished from clinically significant effects which are considered adverse effects.

Clinically significant effects should be considered adverse effects for anyone not under the supervision of a physician prescribing this drug for a specific medical condition. These would have associated Lowest-Observed-Adverse-Effect Level (LOAELs). Quite often, the LOAEL for these effects is used as the Point-of-Departure (PoD) for derivation of the ADE value.

5.3.3 *Dose-Response Assessment*

During the hazard characterization process, all effects potentially attributed to a compound should be documented. Each effect, whether considered adverse or not, has a dose-response relationship. In general, as the dose increases, the incidence and severity of the effect increases.

For systemic toxicity endpoints, there is a dose below which no effects are expected. This is often referred to as the threshold for toxicity.

[1] PubMed.gov is part of the US National Library of Medicine (NIH). PubMed comprises more than 19 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full text content from PubMed Central and publisher websites. http://www.ncbi.nlm.nih.gov/pubmed.

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For some endpoints such as cancer, due to direct damage to DNA, it is often assumed that a threshold does not exist and some effects (e.g., mutations) are possible at low doses. In this case, it is necessary to determine the acceptable level of response for the effect (e.g., a 1/100,000 excess cancer risk). It should be noted that this may be viewed as a conservative approach given that there are DNA repair mechanisms that may reverse the mutations and immunosurveillance mechanisms that prevent cancers from developing.

5.3.4 *Establishment of the NOAEL or Benchmark Dose*

For most toxicity endpoints, there is a clear dose-response relationship for the critical effect. The aim is to define the NOAEL for the critical effect, which may be used to derive the ADE. The application of adjustment factors (see Section 5.3.5) results in ADE values that are unlikely to produce any undesirable compound-related effects.

It may not be possible to define the NOAEL for some toxicology data sets, and therefore, it may be necessary to derive the health-based limit using a LOAEL. This occurs when statistically significant adverse effects are observed at the lowest dose used in a study. The Benchmark Dose (BMD) can be used in this situation.

The BMD is a value, equivalent to a NOAEL, that is derived mathematically by fitting a curve to the dose-response data for the critical effect. (Software to derive a BMD is available on the US EPA Website [45]. The BMD_{10} is defined as the dose that corresponds to a 10% response rate, the minimum level of response typically detected by standard toxicology studies. The statistical lower bound on the BMD_{10} ($BMDL_{10}$) is often used in risk assessments as a surrogate for a NOAEL. Caution should be taken when extrapolating well below the observable range. (A tutorial and a technical guidance document on the use of the BMD are available on the EPA website.)

5.3.5 *Application of Adjustment Factors*

Health-based exposure limits, such as ADE values, are derived by dividing the NOAEL for the critical effect (after adjusting for body weight, e.g., 50 kg) by various adjustment factors (also termed assessment, safety, or uncertainty factors) to extrapolate to the “true” no effect level in the subpopulation of interest (e.g., elderly patients). Depending on the assumptions about the composition of these subpopulations, different adjustment factors may be used; however, the goal is to protect the most susceptible individuals.

The application of adjustment factors to NOAELs is an accepted approach for non-carcinogens, but is also used for compounds that cause cancer by non-genotoxic mechanisms (see discussion below). It is a policy decision within an organization as to whether an adjustment factor or linear extrapolation approach should be used in a given situation. Regardless of the approach employed, only peer reviewed methods that have been validated through use and experience, should be used to set safe levels of exposure.

The NOAEL is typically derived from a single key study of a relatively small number of animals or humans. Adjustment factors have been defined for each of the main sources of uncertainty and variability as described in this Chapter. These are multiplied together to form a Composite Adjustment Factor (AF_C) that is used in the denominator of the general equation used to set health-based limits (see below).

The ADE is used to derive swab or rinse limits for cleaning validation purposes as well as for other assessments of cross-contamination. In order to apply ADE values to specific subpopulations, further adjustments may be required to address various sources of uncertainty and variability, as well as differences in bioavailability when extrapolating between different routes of exposure. Ideally, the ADE is based on the data for the route that it will be applied to in the evaluation. If route-to-route extrapolation is necessary, a sound scientific rationale is required to support application to a different route.

Calculation of the Acceptable Daily Exposure (ADE) Value

$$\text{ADE (mg/day)} = \frac{\text{PoD} \times \text{BW}}{AF_C \times \text{MF} \times \text{PK}}$$

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Where: ADE = Acceptable Daily Exposure (mg/day)
PoD = Point-of-Departure (e.g., NOAEL, LOAEL) (mg/kg/day)
BW = Body Weight (kg)
AF_C = Composite Adjustment Factor
MF = Modifying Factor
PK = Pharmacokinetic Adjustment(s)

For comparison, the following equation is used in the EMA guideline on setting health-based exposure limits. Individual assessment factors F1 to F5 are included for reference, where appropriate, in Table 5.2.

$$PDE = \frac{NOAEL \times BW}{F1 \times F2 \times F3 \times F4 \times F5}$$

A number of publications discuss the scientific basis for the adjustment factors discussed below and the process for deriving ADEs (Naumann and Weideman, 1995 [39]; Sargent et al., 2013 [42]; Sussman et al., 2016b [44]). Alternative factors may be used if supported by available data for a specific compound and a sound scientific rationale. The use of specific default values for adjustment factors is a policy decision and should be based on generally accepted practices and data in the literature. Toxicological expertise is normally required to determine the appropriate adjustment factor(s) to apply.

5.3.5.1 Addressing Sources of Uncertainty Using Science-Based Adjustment Factors

Table 5.2 shows the correspondence between the various adjustment factors commonly used in human health risk assessment and the EMA guidance on setting health based exposure limits. For each factor discussed below, the similarities and differences, albeit minor, will be identified. The experience of a qualified toxicologist is required to decipher the nuances implicit within each factor. As pointed out in the EMA guidance [5], deviation from the main approach to deriving safe levels may be appropriate if adequately justified.

Table 5.2: Adjustment Factors Used in the EMA Guidance and Risk-MaPP

Adjustment Factor	EMA	Risk-MaPP	Comment
Interspecies	F1 = 2 - 12	AF_A = 2 - 12 Allometric Scaling	$BW^{2/3}$ or $BW^{3/4}$ may be used
Intraspecies	F2 = 10	AF_H = 10 or CSAF	Use PK and PD Data when available
Study Duration	F3 = 10	AF_S = 3	< 4 weeks for F3
Severity of Effect	F4 = 1 - 10	Addressed in MF	Overlaps with F5; MF
LOAEL-to-NOAEL	F5 < 10	AF_L = 3	F5 = 10 if severe effects; overlaps with MF
Database Completeness	AF = 10 or Read Across	AF_D = 1 - 10	Missing Developmental and Reproductive Toxicity (DART) Studies
Modifying Factor	MF	MF < 1 - 10	Residual Uncertainties, Severity of effect
Pharmacokinetic Adjustments	Bioavailability Correction	Bioavailability Correction (α), Steady State (S)	Route-to-Route Extrapolation

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a. Interspecies Differences (AF_A or F1): This adjustment factor is used to extrapolate a NOAEL (or LOAEL) from animal studies to a human subpopulation. A common approach is to use allometric scaling, which results in separate values ranging from 2-12 when extrapolating from various species due to differences in body surface area/volume ratios based on $BW^{2/3}$ (Davidson et al., 1986 [46]; Mordenti and Chappell, 1989 [47]). The FDA guidance document on setting doses in initial clinical trials includes specific species extrapolation factors (FDA, 2005 [48]). The US EPA recommends use of $BW^{3/4}$ as more appropriate for allometric scaling (EPA, 2005 [49]), corresponds to a range of values from 2 to 7 for the common species used in toxicology studies.

b. Intraspecies Differences (Interindividual Variability) (AF_H or F2): This factor reflects the variability that exists in the subpopulation of interest (i.e., the most susceptible subgroup) compared to the study population from which the NOAEL was derived in terms of systemic exposure for a given dose (kinetics) and how the body responds (dynamics). These may be considered as what the body does to the chemical and what the chemical does to the body, respectively. The factor for interindividual variability is used to adjust NOAELs derived from animal and human data. In the case of human data, it may be the only adjustment factor that is required. A default adjustment factor of 10 is typically used in the absence of chemical-specific data (see this section for further information) (Dourson et al., 1996 [50]).

c. Study Duration (AF_S or F3) – When the duration of the study used to identify the critical effect is different from the actual exposure scenario, an additional adjustment needs to be made. Reviews of a large number of high quality toxicology studies suggest that a factor of 3 is sufficient to account for the possibility that a lower NOAEL would have resulted if longer term studies were conducted (Weil and McCollister, 1963 [51]; McNamara, 1976 [52]; Lewis et al., 1990 [53]; Lewis and Nessel, 1994 [54]; Kadry et al., 1995 [55]). It should be noted that upward adjustments (i.e., $AF_S < 1$) of the dose may be appropriate when longer duration studies are used to set acceptable doses for short-term exposures. When shorter duration human studies are used as the basis for deriving the ADE, it may not be necessary to adjust for study duration if long-term animal studies show little concern for chronic exposure. In addition to the augmentation by long-term animal studies, it may not be necessary to adjust for short-term human studies if no exacerbation of the critical effect would be anticipated with longer term human exposure/studies (e.g., for a compound that decreases glucose levels). The exposure scenario for the patient receiving the API as a contaminant in another drug should also be considered, e.g., 90-day mail order supply from the same batch.

d. LOAEL to NOAEL Extrapolation (AF_L or F5): The Point-of-Departure (PoD) is frequently the low clinical dose; however, information on pharmacological or toxicological effects below this dose may not be available (e.g., with generic drugs). When only a LOAEL is available from a key study used to derive the ADE, it may be possible to calculate a benchmark dose (see above) to extrapolate an existing dose-response curve downward or, in absence of better data, to apply a factor of 3 to extrapolate from a LOAEL to a NOAEL. This is a best estimate and is derived from analyses of a large number of quality toxicology studies that, due the dose selection decisions in well conducted animal studies, the ratio of the LOAEL:NOAEL rarely exceeds this value (Weil, 1972 [56]; Lewis, 1993 [57]; Abdel-Rahman, 1995 [58]).

e. Database Completeness (AF_D): An additional adjustment factor may be required if the overall toxicity database is incomplete, e.g., if developmental and reproductive toxicity studies have not yet been performed. The EMA guide also makes reference to the possible need for additional “modifying factors” to account for missing data, and specifically mention the lack of data on reproductive and developmental toxicity. This factor is intended to account for the possibility of finding a lower NOAEL once these studies are performed. Available data suggest a factor of 3 for this purpose (Dourson et al., 1996 [50]).

f. Modifying Factor (MF or F4 (Severity)): A modifying factor may also be considered if there is a need to address residual uncertainties not covered by the other factors. It may also be used to account for the severity of effect or the slope of the dose-response curve. These are covered in adjustment factors F4 and F5 in the EMA guide, although it does mention the need for additional modifying factors to address residual uncertainties, e.g., missing reproductive and developmental toxicity data (Note: that this overlaps with AF_D so care needs to be taken not to double count). The modifying factor also allows a way for professional judgment to be applied to address the overall quality of the database and relevance of available studies to human risk assessment. MFs of < 1 to 10 may be used in these cases (Dourson et al., 1996 [50]).

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Pharmacokinetic Adjustments (PK): In certain cases, route-to-route extrapolation may be appropriate when attempting to derive an ADE from a study conducted by a route (e.g., oral) that is different from the potential route of exposure (e.g., parenteral or inhalation). This need for adjustment is specifically cited in the EMA guide. Although direct studies using the relevant route of administration are normally expected, extrapolation using an additional adjustment factor (e.g., bioavailability correction factor often designated as α) may be useful to ensure adequate protection in some situations. An example is an oral drug that has an oral bioavailability of 50%, with an ADE based on oral data, being used to derive cleaning limits for a parenteral drug (Product B) where 100% bioavailability is assumed following administration. In this case, the ADE value would need to be adjusted downward by a factor of 2 to align the corresponding plasma levels following oral and parenteral exposure and to adjust the ADE value appropriately. One scenario where this may be required is a chemical manufacturing operation where APIs for oral and parenteral products are synthesized in the same equipment. Similar adjustments may be necessary when setting occupational exposure limits (see Section 5.4). For more background on bioavailability correction factors and when they should be applied, see Naumann and Weideman, 1995 [39]; Pfister et al., 2014 [59].

The ADE value is intended to be protective for all routes of patient exposure. In certain manufacturing scenarios (e.g., oral solid dosage form manufacturing), only one route of patient exposure is a concern. In these cases, the ADE value could be adjusted, but to avoid confusion, this should be done at a later step in the risk assessment process. Bercu et al., 2013b [60] discuss setting product specific ADE values when information about the subsequent product is known. If a company chooses to use route or product specific ADEs, they must have a robust method to manage the information so that when using an ADE value in a different scenario it is clear if the ADE has already been adjusted for specific scenario(s). Adjustments to acceptance limits may also be needed if the margin of safety is not large enough for the subpopulation of concern (e.g., pediatric patients).

Additional factor(s) may be needed to adjust health-based limits such as ADE values because of the potential for bioaccumulation with repeated exposure. For compounds with long elimination half-times, plasma levels increase with continuous exposure until they reach steady state.

The ADE established using a NOAEL from a short duration study would need to be adjusted downward by a factor (often designated as S) corresponding to the ratio of the plasma level following a short-term exposure to the expected plasma level at steady state following long-term exposure. This adjustment is not necessary if the ADE is established using studies of sufficient length, where the steady state at the maintenance dose is known, since any accumulation has already been taken into account in this situation.

The adjustment factors described above represent current methodologies that are supported by scientific evidence. When non-cancer risk assessment methods were being developed (Lehman and Fitzhugh, 1954 [61]; Dourson and Stara, 1983 [62]), factors of 10 each were considered protective with a high degree of confidence. Despite the fact that more recent assessments have shown that lower values are still adequately protective, default values of 10 are sometimes used to set health-based limits. The fact that they are overprotective compared to science-based limits is not problematic from a health standpoint if the overall goal is to provide protection. However, this practice may lead to the over-design of manufacturing processes and increased manufacturing costs, with no material benefit to the patient.

5.3.5.2 Use of Chemical-Specific Adjustment Factors for Differences in Pharmacokinetics and Pharmacodynamics

During new product development, a significant amount of data on pharmacokinetics and pharmacodynamics are generated. These data can be analyzed to provide insights and to quantify interindividual and interspecies differences in kinetics and dynamics (Silverman et al., 1999 [41]; Naumann et al., 2001 [63]; Sargent et al., 2002 [64]). The use of Chemical-Specific Adjustment Factors (CSAFs) is particularly important for assessment and protection of susceptible subgroups, e.g., children, the elderly, or individuals with liver or kidney dysfunction. CSAFs can be derived by dividing a value two standard deviations above the mean by the mean itself for relevant kinetic and/or dynamic parameters. Meek et al., 2001 [65] recommended guidelines for proper application of CSAFs in risk assessment. CSAFs are intended to replace the default factors where sufficient pharmacokinetic and pharmacodynamic data are available according to the scheme proposed by Renwick (1993, 1999 [66, 67]) and adopted by the World Health Organization/ International Programme on Chemical Safety (WHO/IPCS, 2001, 2005 [68, 35]). Default uncertainty factors, by definition, should be used only in the absence of relevant chemical-specific data.

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5.3.5.3 *Derivation of ADEs for Compounds with Limited Data*

Dolan et al., 2005 [69] published a paper with recommendations on how the "Threshold of Toxicological Concern" (TTC) concept could be applied to relatively unstudied compounds encountered in the pharmaceutical industry. It builds on the approach used by the FDA (termed "Threshold of Regulation") to determine if new food additives would require testing before being approved (FDA, 1995; Munro et al., 1996a [71]; Kroes et al., 2000, 2004 [72, 73]). ICH M7 [7] is also based on this concept as it applies to mutagenic impurities (see below). Bridging from large databases of well-studied compounds, it was concluded that a daily dose of 1.5 µg of a new food additive consumed in the diet, was likely to carry no more than a *de minimis* level of risk. Munro et al., 1996b [74] compiled data for various endpoints and structural classes and created distributions of thresholds of acceptable human exposure derived by applying a 100-fold safety factor to the NOAELs.

Dolan et al., 2005 [69] expanded this concept to include three categories of compounds with limited or no toxicity data:

1. Compounds that are likely to be carcinogenic
2. Compounds that are likely to be potent or toxic
3. Compounds that are not likely to be potent, toxic, or carcinogenic

The corresponding ADEs recommended for these three categories are 1, 10, and 100 µg/day, respectively. These ADEs are intended to be applied when justification is needed to support cleaning validation or extraneous matter evaluations for compounds with limited or no information. The same estimated ADEs can be used for early development compounds based on their limited data sets. The TTC is also being suggested for application to food allergens (Hourihane, 2001 [75]; Flinterman et al., 2006 [76]), skin sensitizers (Keller et al., 2009 [77]), and reproductive/developmental toxicants (Stanard et al., 2015 [78]).

The use of the TTC approach for new compounds with limited available safety data represents a strategy to err on the side of caution that applies a tighter control than may be required once more data become available. That way, any subsequent discovery that new compounds require a lower ADE will already have been addressed. The temporary use of the TTC concept to support preliminary ADE values should be an interim strategy until a formal ADE value can be established.

5.3.5.4 *Extrapolation to an Acceptable Level of Risk for Genotoxic Compounds*

For certain categories of compounds (i.e., direct acting genotoxic compounds), the dose-response curve is assumed to be linear at low dosages and the assumption is that there is no threshold below which adverse effects would not be expected. This is based on the theory that a single change in DNA could lead to a mutation and possibly cancer. For this endpoint, a different approach to the "safety factor" method described above should be used.

It should be noted that the risk-based, linear extrapolation methods described below do not need to be applied to all compounds with positive genotoxicity data. For example, there are cases where the mechanism of action does not clearly indicate the compound causes direct DNA damage, and *in vivo* carcinogenicity studies are negative. This may also be true for aneugens (compounds that affect the number of chromosomes). In this case, the *in vivo* data should take precedence over the *in vitro* or *in vivo* genotoxicity assays which, typically, are performed at very high concentrations or doses. The application of adjustment factors to a NOAEL or $BMDL_{10}$ from the *in vivo* carcinogenicity study would be appropriate.

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With an alternative risk-based method, it is possible to establish acceptance criteria for genotoxic compounds based on extrapolation to a dose that corresponds to a *de minimis* level of risk. Use of linear extrapolation methods is a policy decision and should be based on validated methods. The EMA, 2006 [79] and Muller et al., 2006 [80] recommendations on setting acceptable levels for genotoxic impurities in pharmaceutical products assume that 1 cancer case per 100,000 is sufficiently close to background to be considered acceptable, based on a patient risk/benefit analysis. Using this assumption, a daily dose of 1.5 µg/day for lifetime exposure to a genotoxic impurity, would be permitted in a new pharmaceutical product that will be chronically administered if it cannot be avoided. Higher levels are proposed for shorter duration exposure, e.g., up to 120 µg/day for APIs used in clinical trials lasting less than one month. As discussed above, ICH M7 [7] has adopted this approach for mutagenic impurities. Note that the 1.5 µg/day value is essentially the same as the 1 µg/day value recommended by Dolan et al., (2005) [69] for genotoxic compounds that are likely to be carcinogenic.

BMD software (see Section 5.3.4) can be used to model tumor data to derive a Point-of-Departure (PoD) (e.g., $BMDL_{10}$), from which it is possible to extrapolate to an acceptable level of risk (e.g., 1 in 100,000). Fiori and Meyerhoff, 2002 [81] have also made recommendations for deriving acceptable levels for genotoxic compounds, including making adjustments for less than lifetime exposure. Bercu et al., 2013b [60] and Callis et al., 2010 [82] have also provided guidance on how to apply the TTC concept to address special exposure scenarios involving genotoxic compounds.

5.3.5.5 Setting Acceptable Levels of Exposure for Sensitizers

The term “highly sensitizing compounds” is used in a number of GMP guidelines, usually within the context of product segregation or dedicated facilities for penicillin and other beta-lactam antibiotics. This section provides a rationale supporting the manufacture of sensitizers, **excluding beta-lactam antibiotics,** in a multiproduct manufacturing facility.

Sensitization should be included in the toxicological endpoints considered when setting an ADE value. For some types of sensitizers (e.g., dermal sensitizers), it is possible to define a non-sensitizing dose and this NOAEL could be used to establish an ADE value using the “safety factor” approach, e.g., for topical products. For other types of sensitization that are more systemic in nature (e.g., respiratory sensitizers and drug allergy), where a NOAEL is not easily identified, alternative risk-based approaches to establishing a safe level of exposure should be used.

The underlying mechanisms of sensitization reactions, which are immunologically-based responses, are generally well understood and it is known that there is a dose-response for both induction and elicitation of allergic reactions. While thresholds are believed to exist for both induction and elicitation, these can be very low, and the challenge is defining a level of exposure that is not expected to elicit a reaction in the most sensitive individuals.

Dermal and Respiratory Sensitizers

Dermal sensitization is a cell-mediated (Type IV) delayed hypersensitivity response that requires a compound to be absorbed through the skin and to interact with specialized immune cells (e.g., Langerhans cells and T-lymphocytes) in the skin and associated lymph nodes. Like humoral immunity, due to memory in T-cells (in this case), an allergic reaction may result upon subsequent exposure following initial induction of a sensitization response. Data from Human Repeat Insult Patch Testing (HRIPT) and the murine Local Lymph Node Assay (LLNA) can be used to assess the potency of dermal sensitizers.

These data also are used to perform risk assessments demonstrating the safety of topically applied pharmaceutical and cosmetic products. A similar approach can be used to define levels of surface contamination that are unlikely to induce dermal sensitization.

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Respiratory hypersensitivity is an immune-mediated humoral allergic response. In this case, it is described as an IgE-mediated Type I immediate hypersensitivity response, and involves macrophages and B-lymphocytes. Following induction of sensitization, with generation of specific B-cell memory and antibody generating capability, subsequent exposure can elicit a response that involves histamine release by mast cells and other accessory cells culminating in allergic responses that may include bronchoconstriction, angioedema, urticaria, and possibly anaphylaxis and death. Induction of respiratory hypersensitivity can result from dermal exposure, as in the case of small molecular weight chemicals such as 2,4-toluenediisocyanate, but also from inhalation or parenteral administration of large molecular weight compounds such as proteolytic enzymes. Compared to skin sensitizers, it is more difficult to set a safe level of exposure to prevent induction of respiratory sensitization. There are no validated animal tests available for this endpoint; however, several models are in development. Epidemiological studies that provide data on antibody titers, pulmonary function measurements (e.g., FEV1), bronchial challenge, and prevalence of symptoms are required to set safe levels of exposure.

Beta-lactam Antibiotics

The FDA and other agencies, such as EMA, PIC/s and ANVISA, expect that dedicated facilities are used for the manufacturing and processing of beta-lactam antibiotics. The prohibition of manufacturing penicillin in the same facility with other products (even other beta-lactam antibiotics) is based on the concern that trace quantities of penicillin can potentially cause a serious anaphylactic reaction, and possibly death, in penicillin sensitive patients. Due to the severity of these effects, regulators consider the risks associated with exposure of sensitive individuals as a result of human error and other undetected operations or design flaws in a multiuse manufacturing environment, to be too severe to allow the production of beta-lactam products in such facilities. Notwithstanding, ADE values should be developed for beta-lactams that, in certain jurisdictions, are allowed to be co-manufactured with other beta-lactams and for assessing the risk of beta-lactams to other compounds when processed on a multiproduct site.

5.4 Setting Occupational Exposure Limits

The primary purpose of this Chapter is to describe methods to set ADE values for patient protection; however, similar quantitative health-based assessments are performed to set OELs to protect workers handling these substances. The safe level of exposure for patients may be different from that established for workers. This is because the critical effect used to derive the limits may be different due to differences in the anticipated route of exposure, and even where this is the same, the choice of adjustment factors may differ. Workers are generally healthy individuals, whereas patients may be children or elderly, and by definition, have at least one active medical condition.

Adjustments may be necessary to address route-to-route extrapolation, even if the same critical effect is used. For example, an OEL derived from the ADE may need to be adjusted for differences in bioavailability between the route used to identify the critical effect (e.g., oral) and the anticipated route of exposure (e.g., inhalation) (Naumann and Weidmeman, 1995 [39]; Naumann et al., 2009 [83]; Pfister et al. [59], 2014).

If the same assumptions apply regarding the critical effect, susceptible subpopulations, and bioavailability (e.g., 100%), an OEL can be calculated directly from the ADE by dividing the dose allowed by the volume of air breathed by a worker, typically 10 m^3, engaged in light work for 8 hours. Likewise, surface target values (e.g., wipe limits), which are used for worker protection, can also be derived by dividing the dose permitted in 8 hours at the OEL (i.e., OEL × 10 m^3) by a standard surface area (e.g., 100 cm^2), but this is often viewed as a convenient, if not arbitrary, approach for assessing exterior equipment and facility surfaces for worker protection purposes. They are perhaps best used to evaluate whether containment equipment is preventing contamination of the workspace. The same caveats for OELs apply to wipe limits with regard to the appropriateness of the direct use of the ADE. While it may be tempting to use wipe limits to assess the potential for cross-contamination, it is important to emphasize that they are developed for worker safety purposes. Any other use must be done within the context of a risk assessment for patient safety (cross-contamination) when considering specific plausible pathways of exposure to product.

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