



Baseline®
**PHARMACEUTICAL
ENGINEERING GUIDE**
FOR NEW AND RENOVATED FACILITIES

Volume 1
Active

Pharmaceutical Ingredients

Second Edition / June 2007

Revision to Bulk Pharmaceutical Chemicals





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Disclaimer:

This Guide is meant to assist pharmaceutical manufacturers in the design and construction of new and renovated facilities that are required to comply with the requirements of the US Food and Drug Administration (FDA). The International Society for Pharmaceutical Engineering (ISPE) cannot ensure, and does not warrant, that a facility built in accordance with this Guide will be acceptable to the FDA.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Dear Colleagues:

The Food & Drug Administration is pleased to cooperate with the International Society for Pharmaceutical Engineering in the development of this *Baseline* Pharmaceutical Engineering Guide for Bulk Pharmaceutical Chemicals Facilities. This Guide is an excellent example of how FDA and industry can collaborate in areas where both the industry and the public can potentially benefit from such partnering efforts.

This document covers engineering aspects of building new bulk pharmaceutical chemical manufacturing facilities. FDA has no written guidance in this area, but we welcome cooperative efforts and the dedicated intensive work demonstrated by the engineers who voluntarily initiated the development of this Guide.

This Guide is neither a regulation nor a standard. We also wish to emphasize that this Guide is intended for new facilities and will not be considered a *Baseline* against which to measure existing facilities. It should be helpful to the engineering profession and the industry in designing bulk pharmaceutical facilities.

FDA is pleased with the development of this document and we look forward to a continued partnership as future *Baseline* Pharmaceutical Engineering Guides are developed.

A handwritten signature in cursive script that reads "Sharon Smith Holston".

Sharon Smith Holston
(Deputy Commissioner for External Affairs)

Foreword

For many years, the pharmaceutical industry has experienced a ratcheting effect in the cost of new facilities. These increases in cost have been driven in part by uncertainty about the requirements for regulatory compliance. The absence of a consistent and widely accepted interpretation of regulatory requirements has led to “creeping incrementalism.” The practice of discretionary investment in plant features that are neither required nor indicated has led to increased cost, longer facility construction and qualification times, and in many cases, delays in bringing new products to market.

In May 1994, engineering representatives from the pharmaceutical industry engaged in a discussion with the International Society for Pharmaceutical Engineering (ISPE) and the US Food and Drug Administration (FDA). That first discussion led to a plan to create a family of nine facility engineering Guides, now known as the *Baseline*® Pharmaceutical Engineering Guides. In November 1994, the ISPE sanctioned the beginning of this important project and the first, “Bulk Pharmaceutical Chemicals,” was published in June 1996. The second, “Oral Solid Dosage,” was published in 1998. The third, “Sterile Manufacturing Facilities,” was published in early 1999. The fourth and fifth *Baseline*® Guides, “Water and Steam Systems” and “Commissioning and Qualification,” were published in 2001. The sixth such Guide, covering Biopharmaceutical Manufacturing Facilities, was published in 2004. The seventh *Baseline*® Guide, covering Packaging, Labeling, and Warehouse Facilities, is expected to be published in the second quarter of 2007.

This is the second edition of ISPE’s *Baseline*® Pharmaceutical Engineering Guide for New and Renovated Facilities Volume 1 “Active Pharmaceutical Ingredients.” It was the first of the *Baseline*® Guide series to be produced and is now the first to be revised. This revision is prompted by a number of developments within the industry requiring the guidance to be realigned and refreshed. One of the realignments is the change in the title of the Guide from Bulk Pharmaceutical Chemicals (BPCs) to Active Pharmaceutical Ingredients (APIs) to reflect more current and global practice. A more thorough discussion of the terms API and BPC is included in Section 1.2 of this Guide. Each *Baseline*® Engineering Guide was created by, and is owned solely by, ISPE. The FDA provided comments on this and previous Guides, and many of their suggestions have been incorporated.

As with the prior Guides, the “Active Pharmaceutical Ingredients” *Baseline*® Guide has been sponsored by engineering executives from owner companies, the FDA, and ISPE senior management. Overall planning, direction, and technical guidance in the preparation this Guide was provided by a Steering Committee of seven people, some of whom were involved in earlier Guide projects. The Guide itself was produced by Task Teams of well more than 40 individuals who expended a great deal of their own time in its preparation and development. An effort was made to not replicate materials and issues already addressed in other Guides, most notably the Commissioning and Qualification Guide. The reader is referred to related ISPE Technical Documents for a complete discussion of the “support” issues affecting the design and operation of Active Pharmaceutical Ingredients Manufacturing Facilities.

Acknowledgements

This Guide was developed by an integrated US-European team under the **co-leadership** of **Simon Shelley** of GlaxoSmithKline and **Patrick Wong** of Bristol-Myers Squibb Co.

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1 Introduction

1 Introduction

1.1 Background to the Revision

The design, construction, commissioning, qualification, and validation of pharmaceutical facilities are significant challenges for manufacturers, engineering professionals, and equipment suppliers. In most cases, these facilities are required to follow cGMPs, while remaining in compliance with other governing codes, laws, and regulations.

The cost of bringing these facilities on-line continues to rise, in many cases, due to inconsistent interpretation of regulatory expectations. ISPE and engineering representatives from the pharmaceutical industry have entered into a partnership with the US Food and Drug Administration (FDA) to enhance understanding of Baseline cGMP expectations for facilities. This Guide is intended to offer a consistent interpretation, while still allowing a flexible and innovative approach to facility design, construction, commissioning, qualification, and validation.

This is the second edition of ISPE's Baseline® Pharmaceutical Engineering Guide for New and Renovated Facilities Volume 1 – Bulk Pharmaceutical Chemicals, (now entitled Active Pharmaceutical Ingredients), which was originally published in June 1996. It was the first of the Baseline® Guide series to be produced and is now the first to be revised. This revision is prompted by a number of developments within the industry requiring the guidance to be realigned and refreshed. This revised Guide builds on the original principles, but also incorporates and builds on new guidance such as:

- ICH Q7 (Section 21, reference 1)
- ICH Q9 (Section 21, reference 2)
- GAMP 4 (Section 21, reference 3)
- ISPE Baseline® Pharmaceutical Engineering Guide Series (Section 19, reference 4)
- 21 CFR Part 11 (Section 21, reference 5)
- "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice", issued September 2004
- FDA Draft Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, August 2003

It is recognized that industry standards evolve and this document reflects the understanding of these standards as of the publication date.

1.2 Scope of this Guide

This Guide may be used by industry for the design, construction, commissioning, qualification, and validation of Active Pharmaceutical Ingredients (APIs) facilities. It is neither a standard nor a detailed design Guide. It is not intended to replace governing laws or regulations that apply to facilities of this type. It also is not intended to apply to existing facilities, which may fall short of the **baseline** described. The use of this Guide for new or existing facilities is at the discretion of the facility owner or operator; however, the principles can be followed for refurbishments and renovations. The question of how much refurbishment or renovation constitutes a new facility will be unique to each project and should be assessed by the owner or operator, and the Guide used accordingly.

The original 1996 version of this Guide was written in the United States and was intended primarily for facilities supplying BPCs to the US. However, with adoption of ICH Q7 and this revision of the Baseline® Guide to Bulk Pharmaceutical Chemicals, the scope is expanded to include international API manufacturing.

The scope of the Guide now covers Active Pharmaceutical Ingredients (APIs) facilities, and includes Bulk Pharmaceutical Chemicals, intermediates, and non-APIs (excipients) facilities.

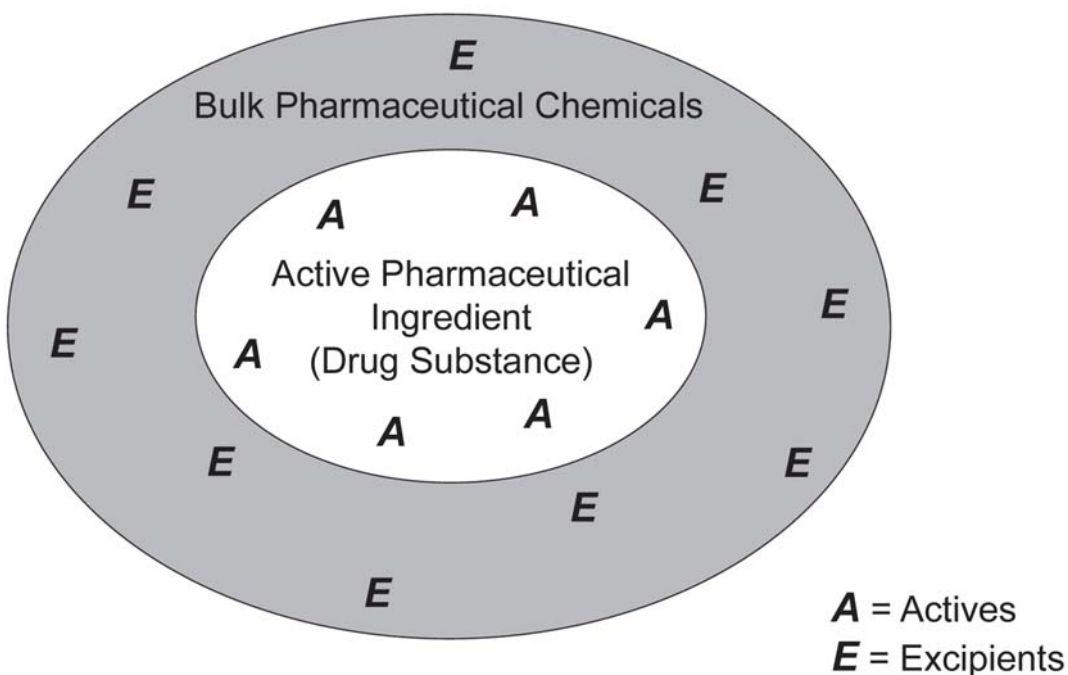
It is important to note that the terms 'BPC' and 'API' are not equivalent terms and should not be used interchangeably. These terms are used specifically in this Guide.

All APIs are BPCs, but not all BPCs are APIs. The term BPC also includes non-APIs (excipients).

To allow alignment to ICH Q7 in the context of this Guide, APIs are considered equivalent to 'Drug Substances'.

Figure 1.1 illustrates the relationship between Bulk Pharmaceutical Chemicals and Active Pharmaceutical Ingredients.

Figure 1.1: Relationship between BPC and API



The scope of this Guide focuses on the manufacture of APIs and intermediates. In addition, there are chapters on scale-up facilities, pilot plants, and non-APIs (excipients). The Guide is applicable to dedicated facilities, as well as multi-purpose facilities, and multi-product facilities. This Guide may not be appropriate for laboratory settings where compounds are synthesized for early development studies.

Bulk biological, secondary manufacturing, and secondary sterile and aseptic processing are the subjects of other Baseline® Pharmaceutical Engineering Guides. This Guide makes reference to, and should be used in conjunction with, other ISPE Baseline® Guides.

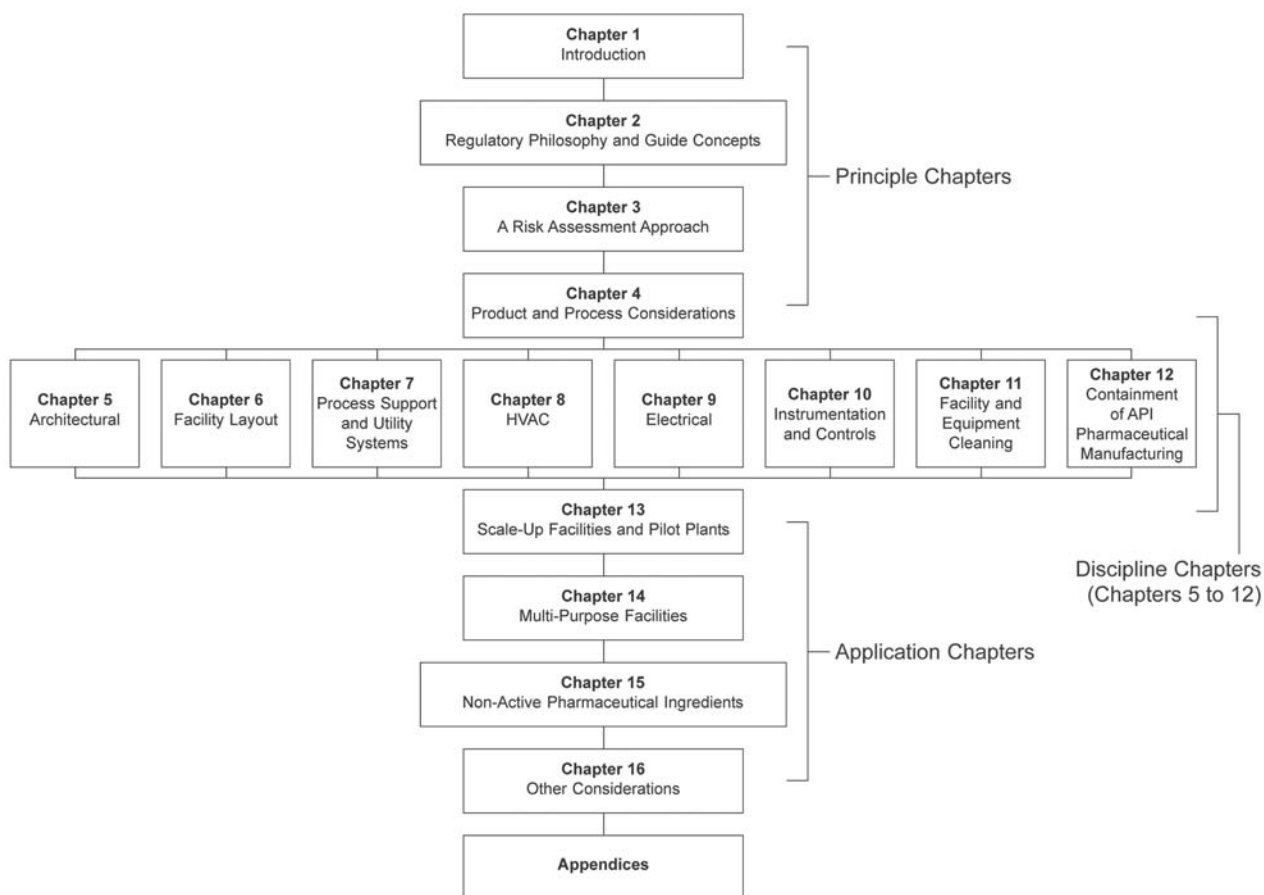
The purpose of this Guide is to focus on engineering issues and how to provide cost effective facilities. Where non-engineering issues are covered (e.g., microbiological topics, operational issues unrelated to the facility), this information is included only to show engineers the importance of such topics, and the impact that they have on facility design.

The Guide has been written in three parts:

- Principle Chapters: explanation of key concepts and tools
- Discipline Chapters: how to apply concepts to the design of the facilities and services
- Application Chapters: when and how to apply the concepts to different types of facilities

An overview of the chapter structure is given in Figure 1.2.

Figure 1.2: Chapter Structure



The concepts proposed constitute a good *Baseline* from which to proceed. All other codes, standards, and governing laws still apply, and are mentioned only for completeness.

1.3 Key Features of the Revised Guide

The concepts listed are defined and used as a basis for guidance.

- Active Pharmaceutical Ingredient characterization
- critical process step(s)
- critical unit operations

- critical process parameters
- critical process parameters
- critical instruments
- critical instruments
- contamination review
- Design Qualification
- intended patient use
- Impact Assessment
- Direct, Indirect, and No Impact systems
- critical and non-critical components
- facility designation
- potential contamination
- Good Engineering Practice
- Levels of Protection
- Process Analytical Technology
- process review
- risk to patient
- understanding of process

A brief explanation of these follows:

The fundamental requirements of the Facility Design for cGMP are driven by the specific API(s) to be produced and the **intended patient-use**. The intended patient-use will help define the **risk to the patient**, which should be taken into account when making facility design decisions. The rationale for inclusion of items in the facility design is documented in the facility **Design Qualification**.

The manufacturer should first define the **Active Pharmaceutical Ingredient characterization**, in terms of the desired chemical and physical properties of the finished API. This characterization, together with **understanding of the process**, is used as the basis for a **process review**, which is used to define the **critical process step(s)**, **critical unit operations**, and the **critical process parameters**.

The critical process parameters for the critical process step(s) affect product quality and should be identified and controlled. The instruments used to control critical process parameters are considered **critical instruments**. This understanding of the process, linked with **Process Analytical Technology**, is one way to provide real-time monitoring and control of process parameters.

The risk to the patient, API characterization, and the understanding of the process can be used to define the critical process step(s) with respect to potential contamination of the API. It is important to understand the facility's intended use and have in mind a clear **facility designation**; this may be multi-use, dedicated, or multi-purpose. This will affect the potential for cross contamination, and hence, identification of further critical process step(s).

A **contamination review** can be conducted once the above information is available. This contamination review identifies the **potential contamination** sources and hence the **Levels of Protection** that are required to prevent potential contamination issues either from equipment or from the environment.

As the ISPE Baseline® Guide to Commissioning and Qualification highlights there is a need to carry out **Impact Assessments** to identify the **Direct, Indirect, and No Impact systems**, as they affect operation of the facility. This allows the identification of **critical components** and **non-critical components**, which aligns to the ICH Q7 definition of 'critical'.

This Guide uses the Impact Assessment technique to identify where the application of **Good Engineering Practice**, using established engineering methods and standards, is adequate to support the cGMP and qualification requirements for the facility.

1.4 Bulk Sterile APIs

This Guide does not address the facility needs of bulk 'sterile APIs.' However, the principles of containment, protection, and facility design outlined in this Guide are fully applicable for processing APIs intended for sterile drug products. It is proposed that more guidance will be made available in the revision to the current ISPE Baseline® Guide on Sterile Manufacturing Facilities.

The rationale for this approach relates to the regulations and standards that apply to 'Sterile Drug Products.' The important principle for consideration is how the cGMP Regulations and standards such as ICH Q7 apply, and at what point in the manufacturing process the 'Drug Substance' is considered 'Drug Product'.

For APIs intended for sterile drug products, the point at which products that are terminally sterilized are considered drug product will be different to that for those that are rendered sterile as a bulk API and then forward processed aseptically.

As a consequence of the above, the handling and treatment of a API prior to sterilization can follow the guidance outlined in this Guide. In applying the tools and guidance, special attention would be given to contamination risks so that any unnecessary challenge to the sterilization unit operation or high resultant endotoxin level is avoided.

Post the sterilization unit operation for aseptically manufactured drug products, the API has been converted effectively into a large volume sterile drug product. The standards of handling, facility layout, finishes, environmental standards, people flows, etc., are covered by Secondary cGMP Guidance, and therefore, are expected to be considered in the revision of the ISPE Baseline® Guide on Sterile Manufacturing Facilities.

1.5 Key Enhancements from the Previous Edition

There are new chapters included in the Guide to address a risk assessment approach, cleaning, containment, pilot plants, multi-purpose plant, and non-APIs (excipients).

1.5.1 Commissioning and Qualification

For details of Commissioning and Qualification, the reader is referred to the ISPE Baseline® Guide on Commissioning and Qualification. Related aspects that are relevant to APIs are discussed in Chapters 2 and 3 of this Guide.

2 Regulatory Philosophy and Guide Concepts

2 Regulatory Philosophy and Guide Concepts

2.1 Introduction

This Chapter suggests ways to implement aspects of an international regulatory philosophy and help project teams establish baselines for the design of process systems and facilities to meet cGMP expectations.

Engineering design should ensure that the APIs produced meet the required levels of quality and purity. A pragmatic approach, coupled with good engineering judgment, should be used when interpreting regulations and choosing the appropriate design.

This Chapter is intended to provide guidance, keeping in mind the current regulatory philosophy, for the design of API facilities.

Specific guidance for the design of non-APIs (excipients) facilities is provided.

2.2 Regulatory Philosophy

GMP guidance for APIs is set forth in **ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients**, which was agreed to by the International Conference on Harmonisation (ICH) in November 2000. ICH Q7 is the accepted cGMP guidance for APIs in Europe, Japan, and the United States (US). It also has been adopted and/or codified in other countries.

EU

ICH Q7 was published as Guidance for API production (human use) in the “Proposal for Annex 18 to the EU guide to Good Manufacturing Practice” (published on the Web site in November 2000, proposal adopted by the commission on 18 July 2001). “The Rules governing medicinal products in the European Union” Volume 4 applies to finished pharmaceuticals. Special guidance on qualification and validation is given in Annex 15.

US

A regulation is set forth by law. Guidance is defined by the Food and Drug Administration (FDA) as their current thinking on a topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations (21 CFR 10.115).

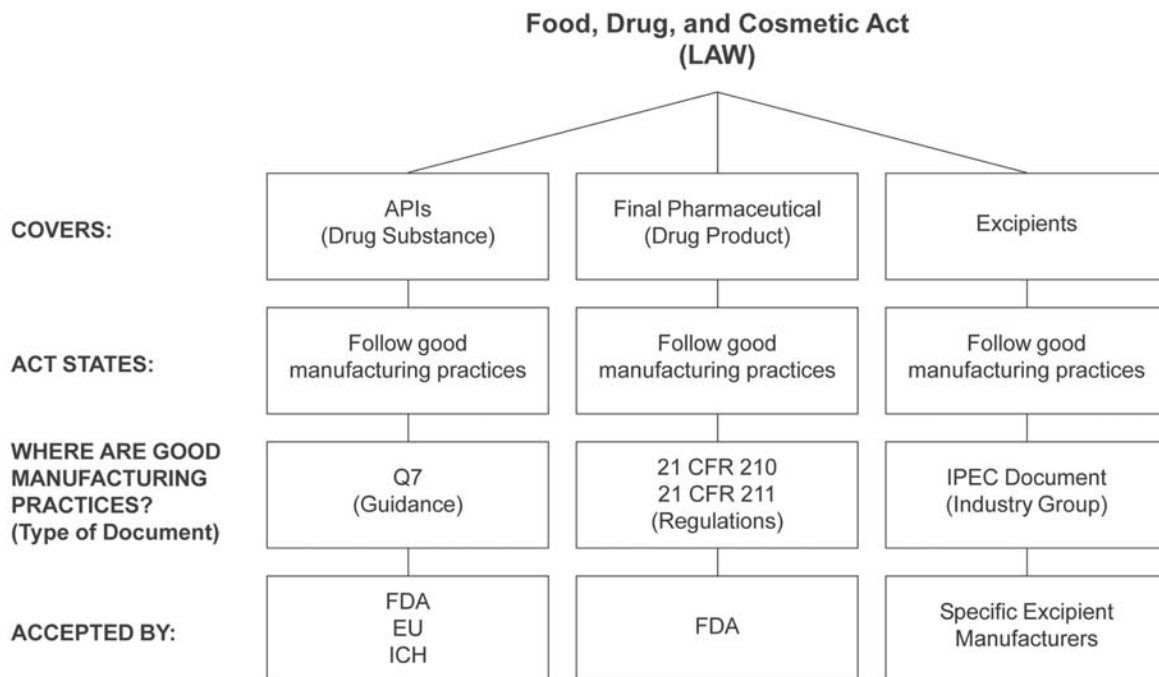
Although there are no “regulations” for API cGMPs in the US, the FDA has utilized ICH Q7 as the guidance document for API cGMPs since 25 September 2001.

The excipient industry has written manufacturing guidance documents and published them through their industry organization, the International Pharmaceutical Excipient Council (IPEC).

The definition of “drug” in the Federal Food, Drug, and Cosmetic Act encompasses APIs and section 501(a)(2) (b) of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with current good manufacturing practice. The cGMP requirements found in the Code of Federal Regulation (21 CFR 210 and 211) apply only to finished pharmaceuticals. There are no regulations covering cGMPs for APIs or excipients. ICH Q7 is used as guidance by the FDA in conducting inspections both within and outside the US.

For sterile API manufacturing, ICH Q7 is applicable to the manufacture of sterile APIs, only up to the point immediately prior to the APIs being rendered sterile. From this point forward, the manufacturing is covered by the finished pharmaceutical regulation (21 CFR 210 and 211).

Figure 2.1: Summary of the US Regulatory Framework



ICH Q7 provides guidance on the cGMP expectations. This ISPE Baseline® Guide provides detailed suggestions on meeting these cGMP expectations.

This Guide is expected to be read in conjunction with several sections of ICH Q7 in relation to topics such as:

- buildings and facilities
- process equipment
- materials management
- production and in-process controls
- validation

The following definitions from ICH Q7 are provided for clarification:

Active Pharmaceutical Ingredient (API) (or Drug Substance)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product, and that when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Intermediates

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide addresses only those intermediates produced after the point that an organization has defined as the point at which the production of the API begins.)

API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Critical

The term critical describes a process step, process condition, test requirement, or other relevant parameter or item that should be controlled within predetermined criteria to ensure that the API meets its specification.

Figure 2.2: Scope of this Guide

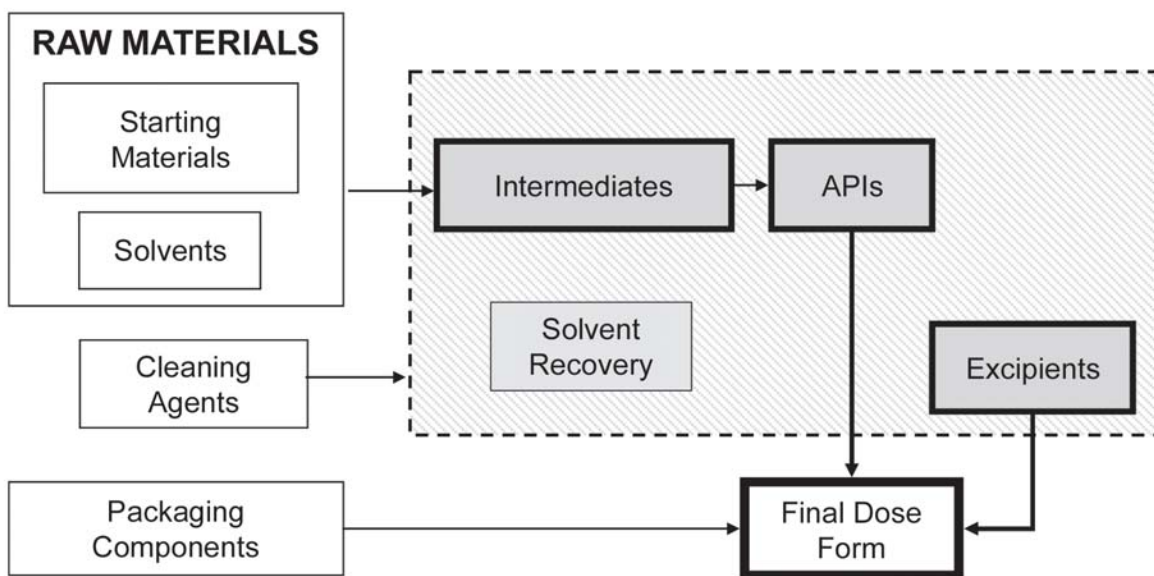


Figure 2.2 illustrates the relationship between APIs, excipients, and dosage forms. The shaded box indicates the types of facilities that are covered by this Guide.

2.3 Guide Concepts and Framework

2.3.1 Approach

This section provides guidance for consideration by manufacturers when planning, designing, constructing, qualifying, upgrading, or operating APIs facilities with regard to establishing consistent and baseline parameters for facility design to meet cGMP expectations. Once these baseline expectations have been met, any additional enhancements desired may be included by the individual manufacturer based upon special requirements or 'added value' to the facility or the product. Specific items covered in this section include:

- intended patient use
- facility designation
- understanding of the process
- characterization of the API

- identification of critical process steps, critical unit operations, critical process parameters
- potential contamination
- Levels of Protection
- when to apply cGMPs to APIs

2.3.2 *Intended Patient Use*

APIs go into a wide variety of dosage forms, including solid orals and liquids, topicals, foot powders, and parenterals. The expected final dosage form will influence regulatory expectations.

The intended use of the API is a major consideration for both the process systems and the facility and knowledge of this will help to identify the risk to the patient.

2.3.3 *Facility Designation*

The manufacturer should identify the intended use of the facility, referred to as 'Facility Designation,' such that the effect of the use of the facility on the product can be identified, assessed, and controlled. The following factors should be considered:

- What APIs are to be manufactured within the facility?
- What equipment configurations are required?
- What is the mode of operation?

Most facilities will be designated to one of three categories (Table 2.1):

Table 2.1: Facility Designation

Type	Facility	Processing Methodology
1.	Dedicated	• Single API and its intermediates in the facility • Same API all the time • The equipment and facility are dedicated • Dedicated operation
2.	Multi-Use	• Facility has a mix of different APIs and associated intermediates, but they use dedicated trains of equipment • Facility has a mix of APIs • Dedicated equipment in a multi-use facility • Concurrent operation
3.	Multi-Purpose	• Trains of equipment and no specific API assigned to any equipment • Different products/changeover within the facility • Multi-purpose facility and multi-purpose equipment • Both concurrent and campaign operation

2.3.4 *Understanding of the Process*

A good understanding of the process is recommended and should be documented in order to identify the critical steps and to make decisions related to process systems and the facility.

API processes can be in many stages of their life cycle when decisions are made regarding process systems and the facility. Additional information about understanding of the process is provided in Chapter 4 of this Guide.

2.3.5 Characterization of the API

In order to define the critical steps in an API process, the manufacturer should characterize the final API, including its impurity profile. This includes all characteristics of the final API, which affect its efficacy, purity, and toxicity. These characteristics may be chemical, physical, or microbiological. Chemical properties include the minimum assay and a maximum percentage of individual impurities (e.g., related substances, inorganic impurities, moisture, or solvent content). Physical properties may include specific particle size range, specific bulk density range, or homogeneity. Microbiological properties include endotoxin and microbial levels.

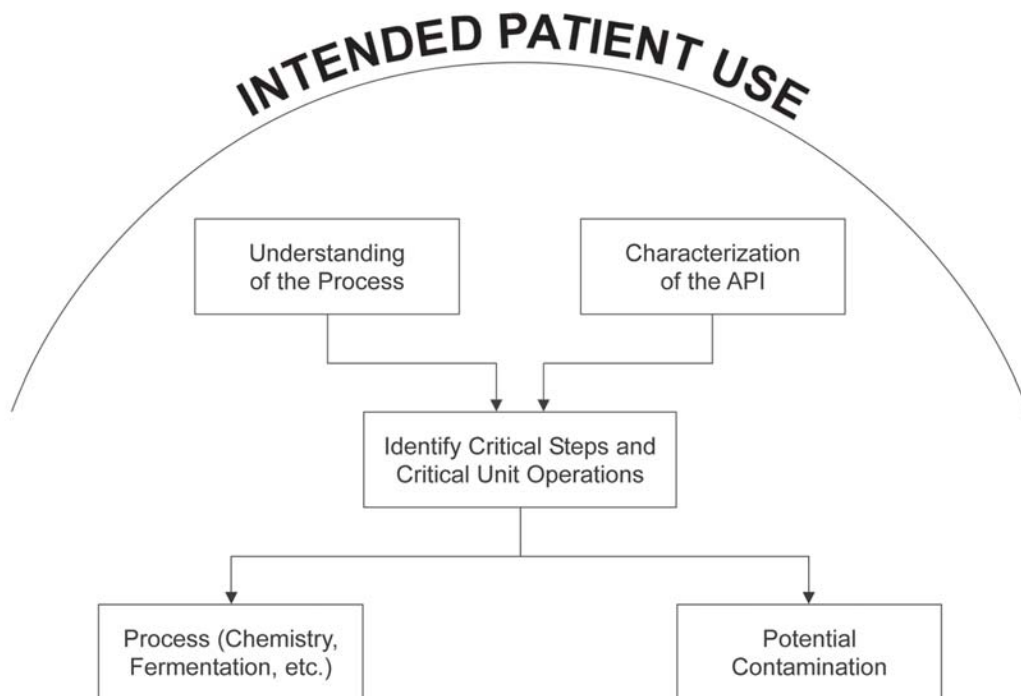
Purchased raw materials and intermediates should be assessed from the point of view of their impact on the purity of the final API. If the purity of a raw material or intermediate is determined to impact the purity of the final API, then that raw material, or intermediate, should be characterized and its impurity profile determined to ensure that it is within specification and consistent from lot to lot.

It may be appropriate to characterize excipients.

2.3.6 Critical Process Steps, Critical Unit Operations, and Critical Process Parameters

The intended patient use, understanding of the process, and the characterization of the API are used to identify the critical steps and critical unit operations. These critical steps and critical unit operations may be critical either with respect to the process itself (chemistry, fermentation, etc.) or with respect to potential physical contamination.

Figure 2.3: Factors for Determining Criticality



Generally, APIs are made in a series of **process steps** (sometimes referred to as process stages (ref. ISA-S88.01-1995)). A process step generally includes one or more unit operations. The output of a process step is either an API or an intermediate. The purpose of each **unit operation** (sometimes referred to as process operations (ref. ISA-S88.01-1995)) is either to make, isolate, purify, size, or package the API or intermediate. Examples of unit operations include reactions, filtration, drying, and milling.

A **critical process step** is one that directly impacts the API and its ability to meet its specification. Within a critical process step, there may be both critical and non-critical unit operations. Each unit operation should be examined separately to determine if it is critical. A critical process step will have at least one critical unit operation. Process validation should focus on the critical parameters within the critical unit operations; it should not attempt to address non-critical unit operations or non-critical parameters. Critical process steps are not limited to the final steps of the API process. A critical process step is one that may cause impurities which end up in the API or which removes impurities that would otherwise end up in the API.

Process steps that follow a critical process step are not necessarily critical.

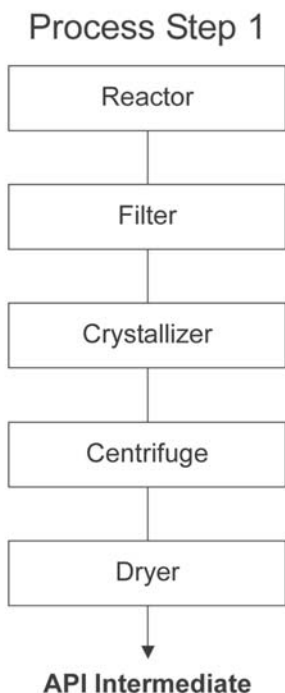
A **critical unit operation** is one that should be controlled within predetermined criteria to ensure that the API meets its specification. A critical unit operation is one after which recovery from process malfunction or contamination is not possible under normal operation. A critical unit operation may be critical due to the chemistry of an API (its impact on purity or formation of impurities) or with regard to protection from physical contamination. Where the unit operation is critical due to chemistry, there are normally one or more critical parameters. Control of the critical parameters keeps the operation within its acceptable range. Where the unit operation is critical for protection from physical contamination, the degree of exposure is controlled. Protection from both internal and external contaminants should be considered.

A **critical parameter** is a processing parameter that directly influences the API characterization or impurity profile. There may be one or more critical parameters for each critical unit operation. Critical parameters may be different for each critical unit operation of the process. For example, drying may be a critical unit operation in two different steps of a process. In one step, the critical parameter may be the level of oxygen; therefore, the critical parameter is controlled by drying under a nitrogen blanket. In the other step, the critical parameter may be the maximum dryer temperature.

Manufacturers should identify the critical parameters based upon their knowledge of the process. This knowledge should be based upon scientific rationale and come from either process development or process history. When validating a critical process step, the critical parameter(s) related to the critical unit operation(s) should receive a high degree of scrutiny.

Therefore, the instruments and systems which measure or control critical parameters are considered **critical instruments** (in the ISPE Baseline® Guide on Commissioning and Qualification these are called critical components) and form part of a Direct Impact system. If the process is under manual control, the operators should follow a standard operating procedure and undergo documented and verified training.

Figure 2.4: Unit Operations within One Process Step



This figure represents an example of a process step made of five unit operations. Please note that this is only an example and does not indicate that every process step will contain these specific unit operations. Actual process steps may contain different or fewer unit operations.

Figure 2.5: An Example of a Three-Step API Process

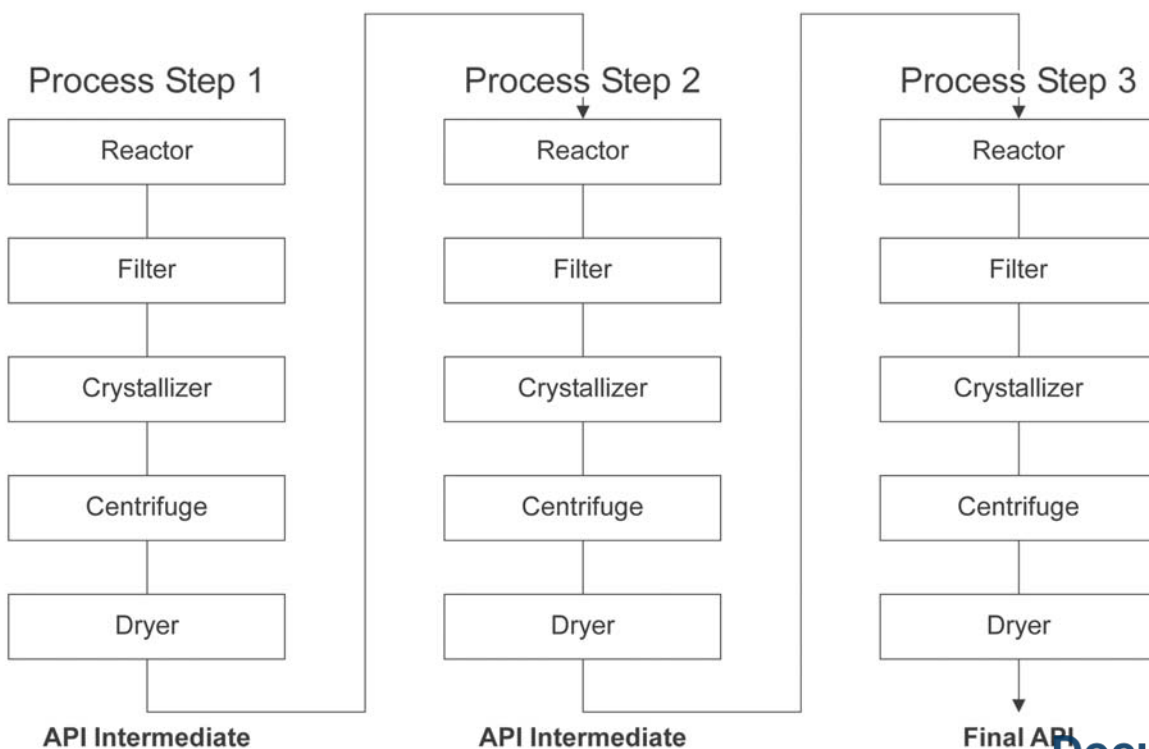


Figure 2.6: Criticality of Process Steps and Unit Operations

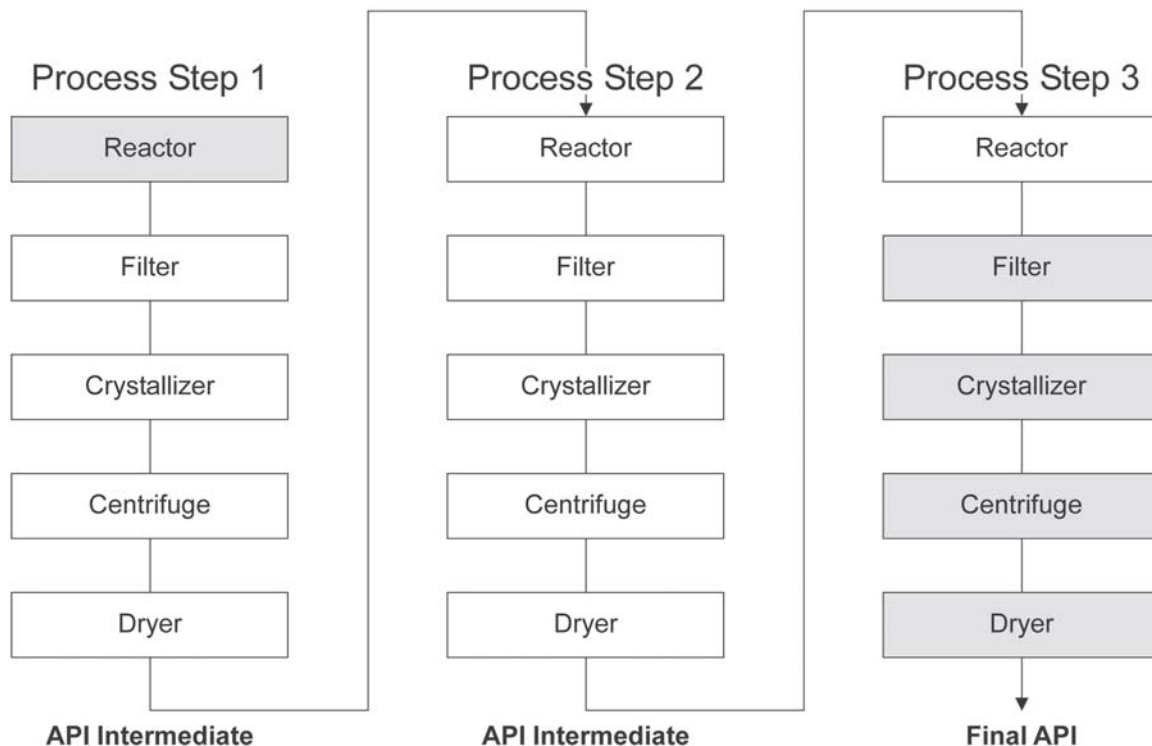


Figure 2.6 shows the same process as Figure 2.5. However in this case, the criticality analysis has been done. In this example, Process Step 1 and Process Step 3 are determined to be critical. Process Step 2 contains no critical unit operations and is not a critical step. Note that just because a process step is critical, not all unit operations within that step are critical. In Process Step 1, the reactor was determined to be the critical unit operation. In Process Step 3, the filter, crystallizer, centrifuge, and dryer were all determined to be critical unit operations. Please note this is an example, criticality should be evaluated for each manufacturing process, for the process steps that make up the manufacturing process, and for the unit operations that make up the critical process steps.

However, some are more complex and may follow branched rather than straight paths (Figure 2.7). In these cases, the critical process steps do not necessarily follow a straightforward path.

Figure 2.7: Branched API Process with Criticality Indicated

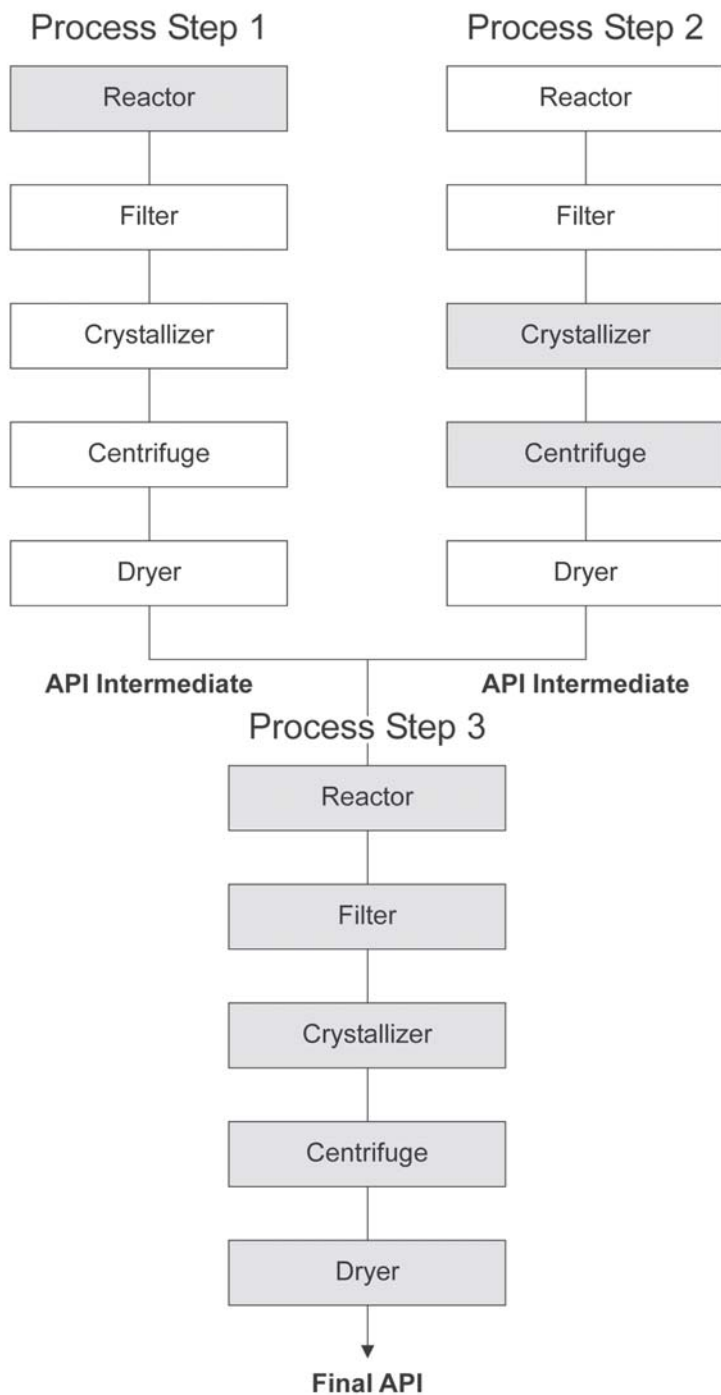


Figure 2.8: Factors for Determining Process Related Criticality

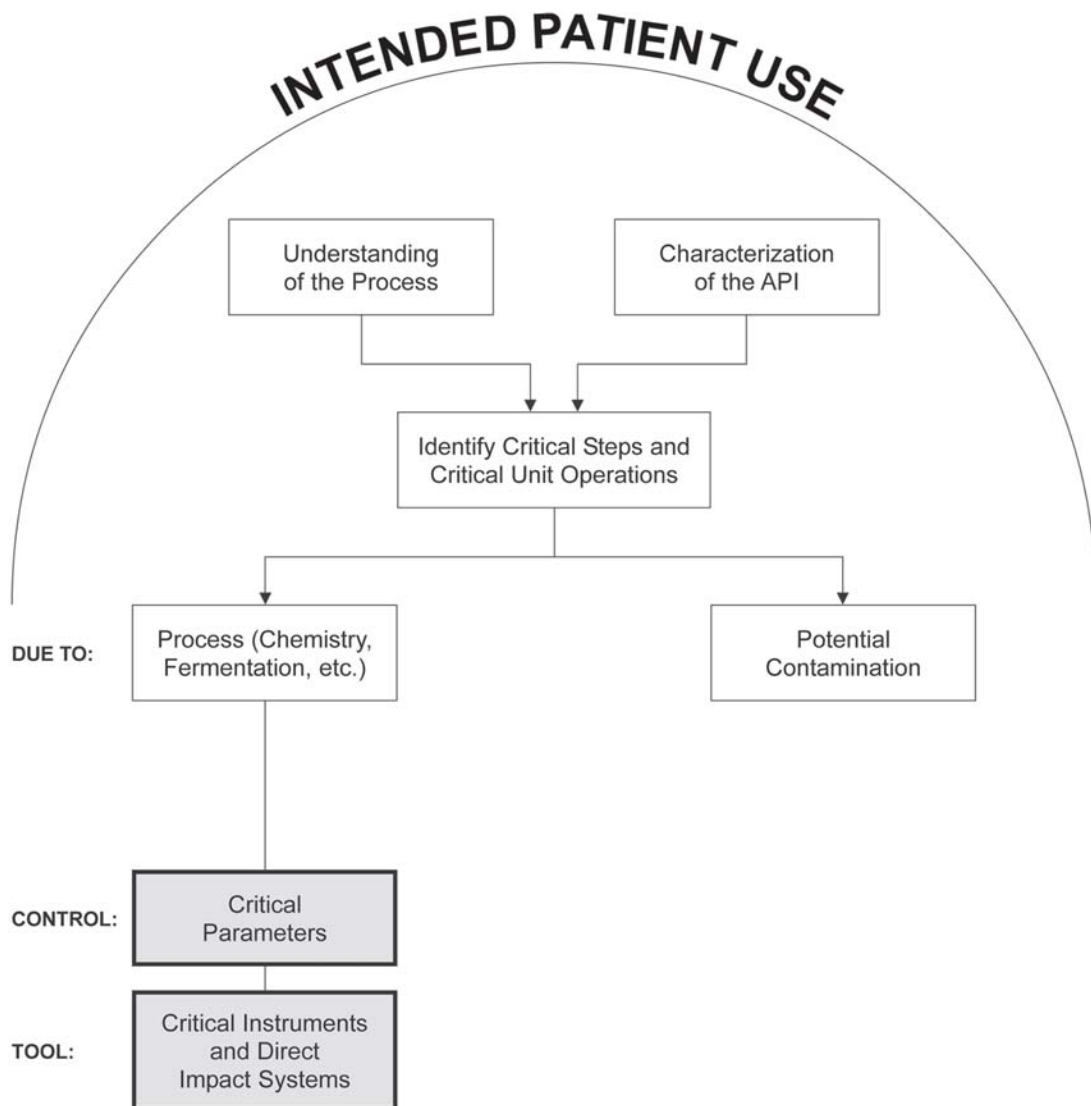


Figure 2.8 illustrates that critical instruments and Direct Impact systems are the tools used to control critical parameters. Critical parameters are the items that need to be controlled in the steps or unit operations that have been determined to be critical.

2.3.7 Potential Contamination

Potential contaminants may contact the API, or intermediate, from sources that are either internal or external to the processing equipment. It is expected that the API and intermediate will be protected from exposure from both of these sources.

Internal contamination can occur either from other materials that are in contact with the API, or intermediate, during the production process, or from the processing equipment that is in contact with the API or intermediate. An example of a material that routinely comes into contact with the API, or intermediate, is nitrogen that is used for creating an inert environment. The cleanliness of such materials should be maintained within defined levels so that they will not adversely affect the API's characterization or impurity profile.

Other internal contamination may come from the materials of construction of the processing equipment. Materials of construction for processing equipment and its internal finish should be compatible with the process materials and stable across the range of processing conditions so that they do not degrade and contribute contaminants to the API or intermediate. The specification of the materials that contacts the process should control the potential contamination from the internal environment. This includes the specification for the material of construction for the equipment (reactor, centrifuge, etc.) and the specification for other components (gaskets, lubricants, etc.) that may contact the API or intermediate. Proper maintenance of the system is important for keeping it in its intended condition.

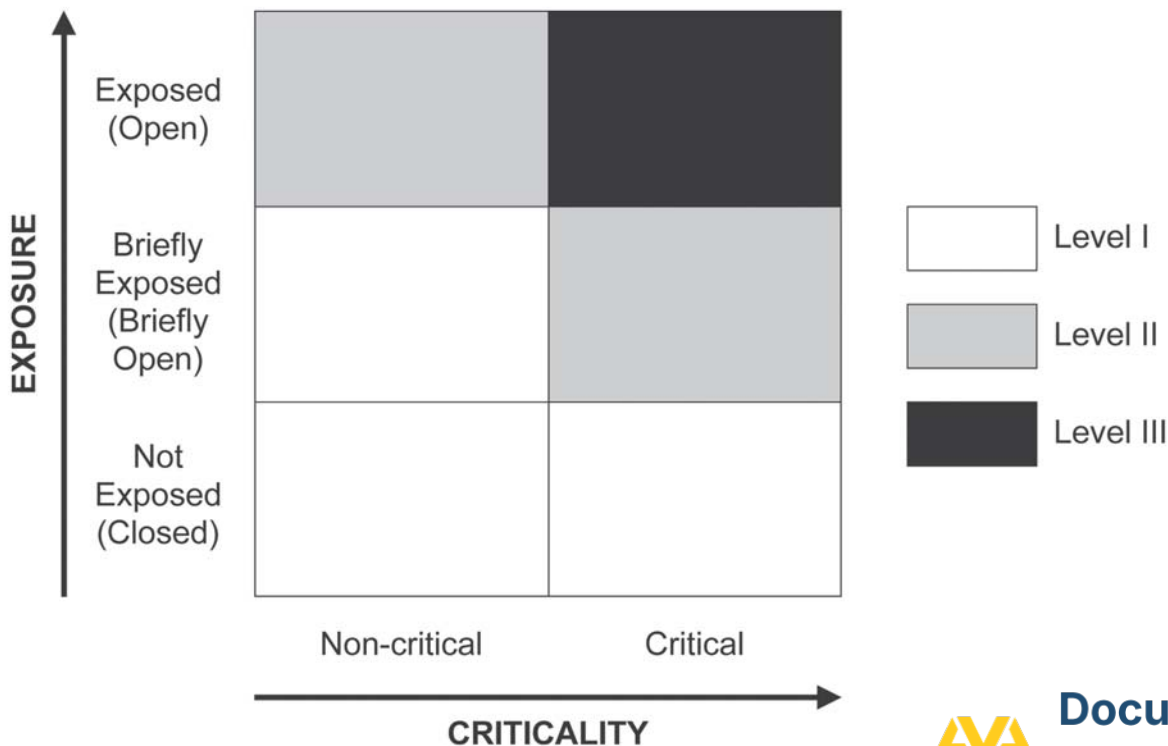
External contamination comes from the external environment to which the API, or intermediate, is exposed. An operation is **exposed** (open) if the API, or intermediate, is exposed to the environment during a processing step, or **not exposed** (closed) if the API, or intermediate, is not exposed to the environment. If a processing vessel is opened for a very short time during processing (in this context of the term "briefly exposed", refers to an opening of a few seconds), the operation is considered **briefly exposed**. If a system is exposed only for a brief period during processing, it may be possible to implement a protective measure so that the operation may be regarded as protected.

With respect to external contamination, critical operations usually occur during or following the isolation of the final API. From this point forward, additional precautions should be taken to protect the API from external contamination. These precautions may include fully closed systems, control of the environment surrounding an opening to the process system, or operating the process system in a controlled environment room or in an isolator.

Figure 2.9 may be used to determine an appropriate Level of Protection with regard to external contamination. The identified Level of Protection may be used as the basis for defining specific environmental condition expectations, such as room air quality, room finish, cleanability, procedures, control, and isolation. Please note that this information is not intended for use in APIs intended for sterile applications (see the revised ISPE Baseline® Guide on Sterile Manufacturing Facilities).

Engineering solutions should consider cGMP, GEP, and personnel requirements.

Figure 2.9: Recommended Levels of Protection



Note: In this context, the term “briefly exposed (briefly open)” means an exposure of a few seconds.

The Three Levels of Protection

There are three ‘Levels of Protection’ designated as:

- Level I – General
- Level II – Protected
- Level III - Controlled

Level I – General

A well-maintained chemical plant that may be located within a building or externally. The area is organized, neat, and clean. The equipment, piping, and instrumentation are maintained in good operating condition.

Example 1: In a step that is critical from the perspective of potential contamination, a reactor is in operation where all materials are charged without exposure to the environment. All sampling occurs without exposing the reactor contents to the environment. The reactor is emptied and its contents are sent to the next operation without being exposed to the environment. Therefore, it is appropriate to perform this operation in a Level I area.

Example 2: In an intermediate step that is not critical from the perspective of potential contamination, the reactor is sampled through an open manway. The manway is opened briefly. The reactor is in a general area of a multi-purpose plant. Procedures are in place to minimize contamination from other operations in the plant (i.e., no dusty operations conducted while the sampling is being done). The area around the manway also has been designed to reduce the likelihood of contamination from the environment, i.e., minimal piping directly above the opening. This is an operation that is not considered critical from a contamination perspective so a Level I area is appropriate.

However, given that it is a multi-purpose plant, procedural controls should be used to prevent contamination by other products.

Level II – Protected

A well maintained chemical plant located within a building with additional protection/precautions to manage the risk of potential external contamination entering the process through **exposed (open) or briefly exposed (briefly open)** processing.

There can be a wide range of solutions that would provide Level II protection based on the actual operation and the potential for contamination. The potential for contamination should be evaluated by an engineer and a solution that affords a Level of Protection commensurate with the risk of potential contamination should be chosen.

Example 1: In an early stage intermediate step that is not critical from the perspective of potential contamination, the intermediate is isolated as a filter cake by closed filtration carried out in a general area. The nature of the filtration device (filter or centrifuge) requires that the cake be removed manually. Therefore, the intermediate would be exposed to the external environment. Since this has been determined to be an exposed non-critical unit operation, Level II protection is appropriate.

Possible ways to accomplish Level II protection include:

- physically moving the filtration device to a room that is separated from other operations that may expose it to cross contamination by other intermediates or drug substances

- instituting and following a procedure to allow only one exposed operation at a time in a room, hence, reducing the risk of cross contamination to the exposed intermediate
- using a portable booth

Example 2: A crystallizer handhole is opened for only a few seconds to charge an ingredient during crystallization. This is a briefly exposed critical operation. A portable charging booth is used to make the addition; therefore, Level II protection is appropriate as this process is briefly exposed.

Level III – Controlled

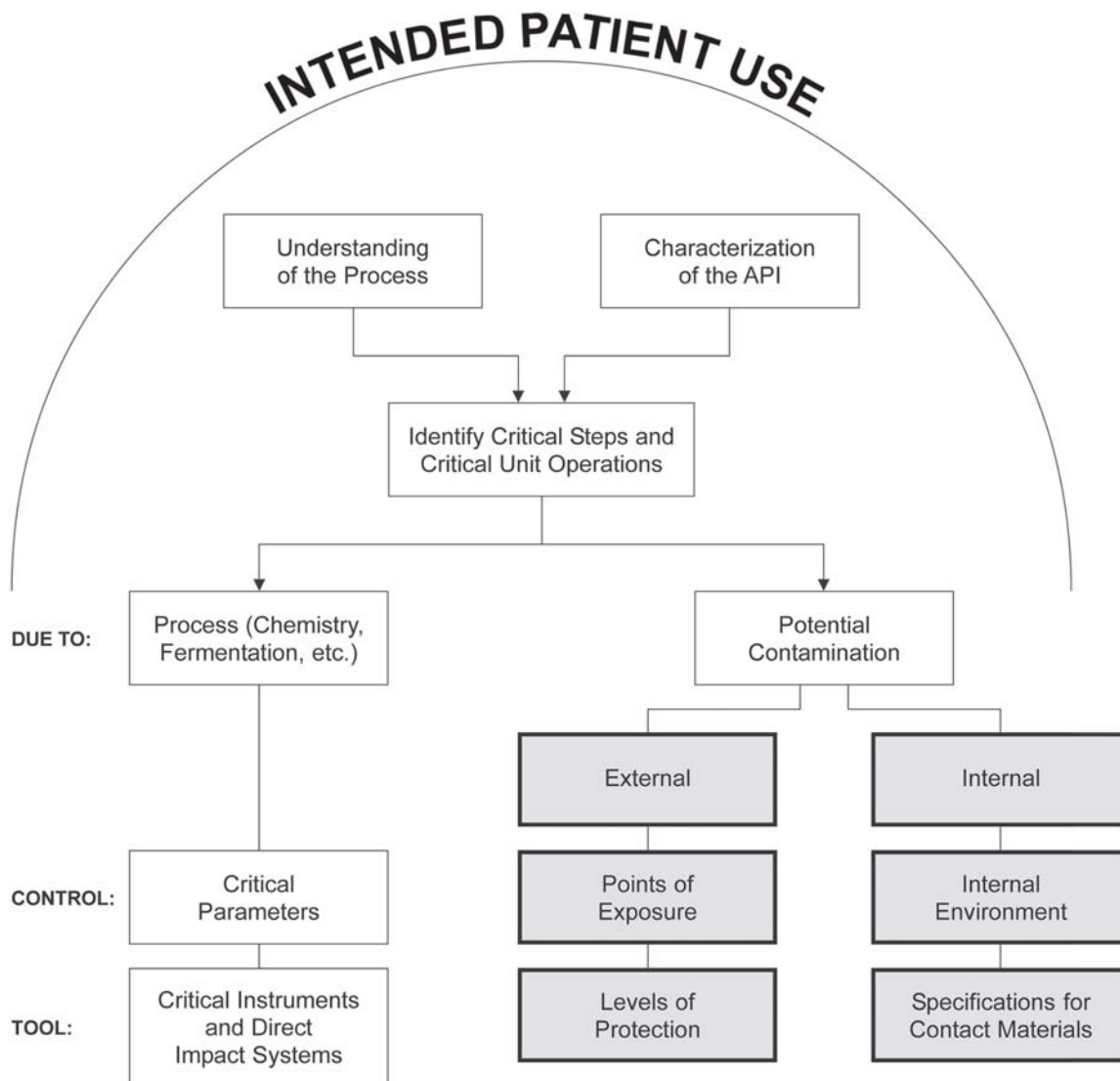
An area, for which specific environmental conditions are defined, controlled, and monitored to prevent contamination of exposed APIs or intermediates.

Example 1: Process material is charged to a dryer in a room where the environmental conditions of temperature, room pressurization, and humidity are controlled and monitored as determined by the specific environmental expectations. The room is readily cleanable. Only one material at a time is dried in the room. The room and the equipment are thoroughly cleaned after each drug substance is handled. The cleaning procedures are validated. This is an open system so Level III Protection is appropriate.

Example 2: Process material is charged to a mill, which is in an isolator in a general area. The material is not exposed to the environment because the milling operation is contained in the isolator and discharged into a container docked to the isolator. The temperature, pressurization, and humidity of the isolator are controlled and monitored. The isolator is thoroughly cleaned after each drug substance is handled. The cleaning procedures are validated. The isolator is the Level III area.

Figure 2.10 illustrates how the Levels of Protection and the material contacting the process are the tools used to control the points of exposure and internal environment, thus, reducing the potential for contamination both internally and externally.

Figure 2.10: Factors for Determining Potential Contamination Related Criticality



Note: In the previous edition of this Guide, Level III was further sub-divided into Level III non-aseptic (Level IIIa) and aseptic (Level IIIb) areas. This sub-division is no longer required as this Guide does not address the facility needs of bulk sterile APIs.

2.3.8 When to apply cGMPs to APIs

When considering the facilities needed to manufacture an API under cGMP conditions, it is important to understand:

- the **process** used to produce the API
- the specifications or **characterization** of the API
- the **intended use** of the API

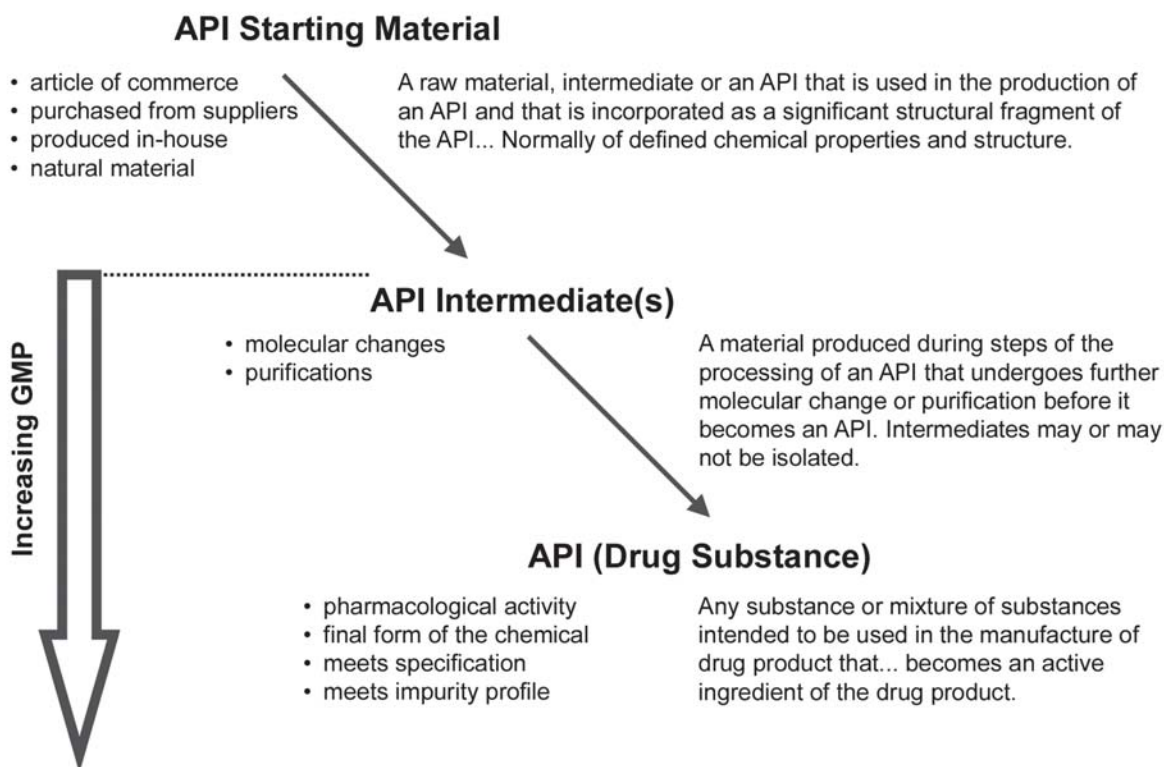
The level of control, protection, and validation that is appropriate to each process should be defined. This should be based upon a sound understanding of the API, how the process and facility impact the purity, reproducibility, and efficacy, and the chemical, physical, and biological characteristics of the API. The specific API's characterization, and which process steps, unit operations, and process parameters will affect that characterization, chemically, physically, or biologically should be determined.

The rationale for the point at which production of the API begins should be designated and documented. For synthetic processes, this is known as the point at which "API starting materials" are entered into the process. For other processes (e.g., fermentation, extraction, or purification), this rationale should be established on a case by case basis. ICH Q7 Table 1 "Application of GMPs in API Manufacturing" gives guidance on the point at which the API starting material normally is introduced into the process.

Appropriate cGMPs as defined in the ICH Q7 Guidance should be applied to API and intermediate manufacturing steps. While applying cGMPs to the entire process may be good business practice, cGMPs as defined in ICH Q7 are expected to be applied with the introduction of the API starting material into the process.

ICH Q7 Table 1 "Application of GMPs in API Manufacturing" illustrates that manufacturers should increase the stringency of cGMP controls as the processing proceeds from early steps to final steps.

Figure 2.11: Application of cGMP



2.3.9 cGMP Interpretation for Equipment Systems

Equipment systems are considered Direct Impact, and should be qualified when they are:

- in direct physical contact with the API, or intermediate, at a critical unit operation
- used to measure, monitor, control, or record a critical parameter

Support systems, such as heat transfer systems, electric power, and non-process contact water for cooling, may not be critical, and therefore, may not need to be qualified. However, any critical parameters that these support systems impact should be qualified.

Any equipment, piping, instrumentation, rooms, environment, control settings, SOPs, or other factors affecting critical parameters should be under change control.

Process validation efforts should be focused on the critical processing steps to achieve quality, purity, and stability of the APIs. All unit operations should be controlled appropriately, but may not need to be validated. Parameters that are unrelated to quality may not need to be included in the process validation.

2.4 Additional Concepts

2.4.1 Design Qualification

Designs of facilities, equipment, or systems should be suitable for their intended purpose. During the design, process decisions may be made that affect the outcome of the design's ability to meet user requirements. By advocating design qualification, ICH Q7 is asking for documentation of the reasons or rationale that led to the final design. There is no specific format for a design qualification. The documentation should be suitable for the facility being designed. The ISPE Baseline® Guide on Commissioning and Qualification discusses an "Enhanced Design Review" which may be used as an approach to Design Qualification.

2.4.2 Process Analytical Technology (PAT)

The FDA is encouraging the use of Process Analytical Technology (PAT) as a possible route for better process understanding and control. PAT is defined as tools and systems that use real-time measurements, or rapid measurements, as well as logic and feedback to achieve control. It may be used during development or manufacturing of pharmaceuticals to monitor or control process parameters. However, using PAT is not obligatory, but the use can lead to increased process understanding and control.

2.4.3 Risk-Based Approach

In recommending a risk-based approach, the FDA is suggesting that manufacturers understand the ultimate risk to the patient and focus on the areas of greatest patient risk. During the design of API facilities, there needs to be an awareness of which areas represent the greatest risk to the API, and therefore, the greatest risk to the patient. The route of administration of the final dosage form has a significant impact on the level of risk to the patient and should be taken into account in making design decisions.

A variety of tools is available for assessing and mitigating risk. The engineering team should decide which, if any, of these tools are appropriate for the design project (Chapter 3).

3 A Risk Assessment Approach



Documents

Document Sharing Hub

3 A Risk Assessment Approach

3.1 Introduction

3.1.1 Introducing Risk Assessment

When the risks to product quality are understood, the designer is able to select appropriate design approaches, as described in other chapters of this Guide, in order to ***eliminate or mitigate the risk to final product quality***.

The purpose of this chapter is to introduce a proposed systematic method of performing a **Risk Assessment**, i.e., a methodology, conducted during the design of the facility to determine, analyze, and manage potential risks to product quality.

Therefore, the main objective of conducting a systematic Risk Assessment is to identify and then manage risks to product quality. This complete focus on compliance also ensures that more effective and efficient facilities are designed. As the perception of risk is different, based on different personal experiences, objective tools and a structured process are used.

The proposed Risk Assessment process contained in this Guide is based on best practice tools and techniques so that it is systematic and objective.

ICH Q9

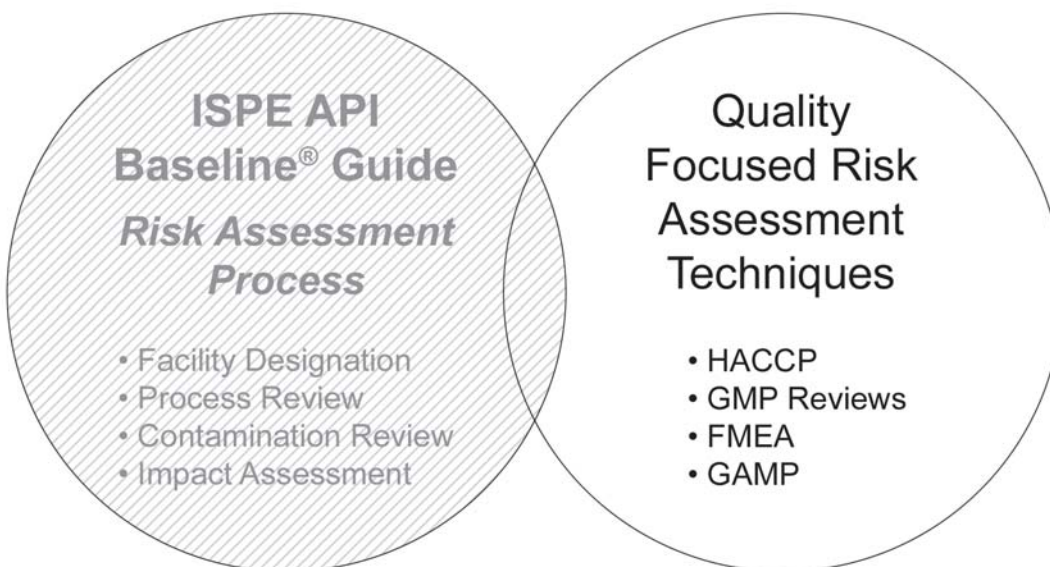
ICH Q9 (Quality Risk Management) provides guidelines on principles and tools for quality risk management that can be applied to different aspects of pharmaceutical quality. In the context of the application of quality Risk Assessment to the design process, the principles in this Guide align with ICH Q9.

3.1.2 Risk Assessment Techniques

The approach proposed uses the high level risk principles common in all Risk Assessment techniques, i.e.:

- What are the categories of risk (where will the risks come from)?
- How likely are they to occur and what would be the impact on product quality?
- Can the risk be completely eliminated (via a suitable mitigation plan)?
- If the risk did occur what could be done to protect product quality (via a suitable contingency plan)?

Figure 3.1: Risk Assessment Techniques



There are many Risk Assessment processes available; some are indicated in Figure 3.1:

- **Hazard Analysis and Critical Control Point Assessment (HACCP):** this is a systematic approach to the identification, evaluation, and control of hazards. It is based around the determination of critical control points, which, if not controlled, may introduce hazardous situations.
- **GMP Reviews:** analogous to the Hazard and Operability review (HAZOP) process (used to identify risks to safety rather than product quality) this Risk Assessment process is based on using “GMP guidewords” to systematically challenge the facility design from a number of perspectives:
 - the facility
 - the processing
 - the product
- **Failure Mode Effect Analysis (FMEA):** is a disciplined design review technique that focuses on actions required to reduce the risk of failure in the process, product, or item of equipment.
- **GAMP:** also uses a structured Risk Assessment process to identify, quantify, and manage risks.

Note: Using the *Risk Assessment Process* contained within this Guide does not negate the need to use other Risk Assessment techniques such as cGMP reviews, etc.

3.1.3 Intended Use of the API

The intended use of the API is extremely important in determining the amount of risk to accept during the API's manufacture. The method of manufacturing of the API is only one factor that affects overall risk to the patient.

For instance, contamination during the processing of an API that ultimately is used in a parenteral would be expected to be much more serious than in an API for which the intended use is as a foot powder. Therefore, the manufacturer that is making the API that will go into a parenteral would accept a lower level of risk of contamination during the processing.

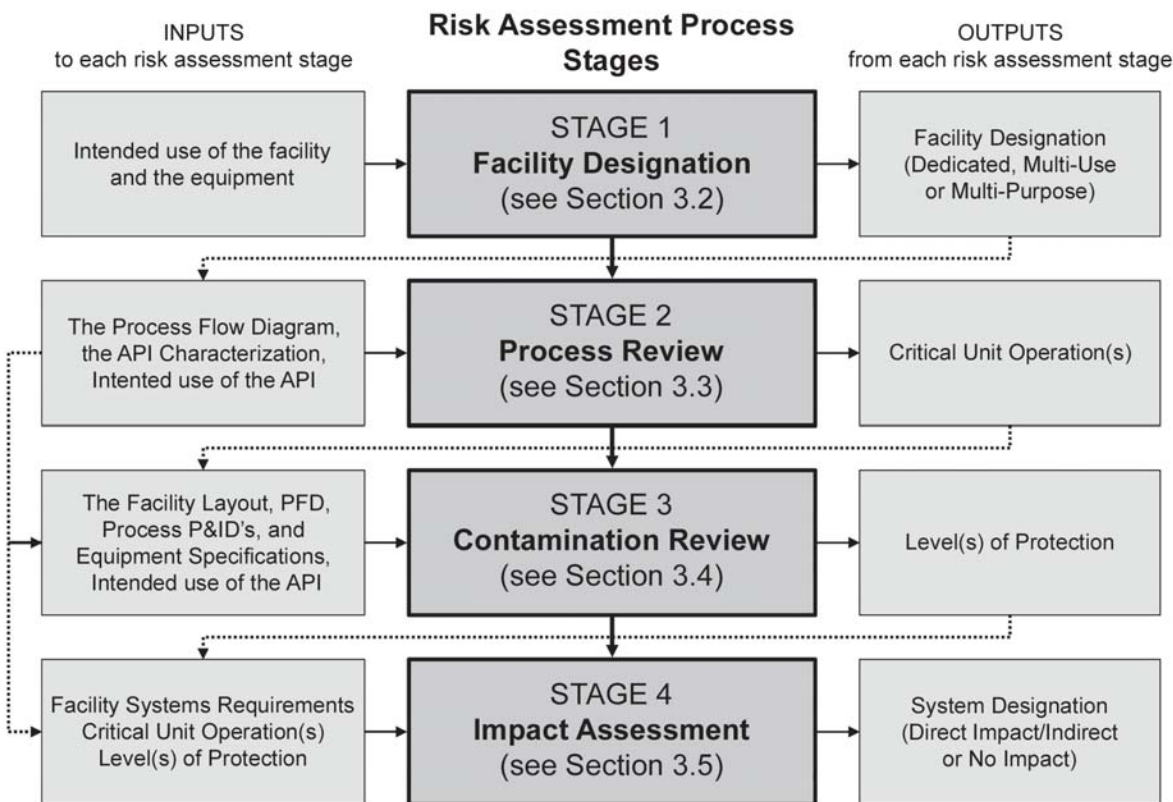
3.1.4 A Risk Assessment Process

Figure 3.2 details the four stages, which form the basis of the proposed **Risk Assessment process**, described in this chapter:

- Stage 1 – Facility Designation
- Stage 2 – Process Review
- Stage 3 – Contamination Review
- Stage 4 – Impact Assessment

An appropriate design approach could be derived from considering each of these categories of risks in turn, analyzing the potential sources of risk and determining the possible consequences.

Figure 3.2: A Risk Assessment Process



There are four potential sources of risk:

- **The process used to manufacture** the API, e.g., synthetic chemistry, fermentation, purification
- **Internal physical contamination**, e.g., product contact materials, seals and lubricants
- **External physical contamination**, e.g., particulates in the air, debris from the facility walls, floors, or the operators
- **Direct/Indirect Impact Systems**, e.g., heat transfer fluid systems, utility systems

Each unit operation will be subject to all four stages of the **Risk Assessment Process** so that each potential source of risk is reviewed, i.e.:

- Stage 2 reviews process risks.
- Stage 3 reviews internal and external contamination risks.
- Stage 4 reviews facility system risks.

3.2 Types of Facility

3.2.1 Stage 1 – Facility Designation

When carrying out a risk assessment, the designer should consider the various uses to which the facility will be put since this may have a crucial bearing on the risks that can arise, e.g., is it:

- dedicated
- multi-use
- multi-purpose

Once the facility designation is confirmed, proceed to Stage 2 of the **Risk Assessment process**.

3.2.2 Types of Facility

The manufacturer should identify the intended use of the facility referred to as facility designation such that the impact of the use of the facility on the product can be identified, assessed, and controlled. The following factors should be considered:

- What APIs are to be manufactured within the facility?
- What equipment configurations are required?
- What is the mode of operation?

Most facilities will belong to one of three categories (Table 2.1).

3.3 Process Review

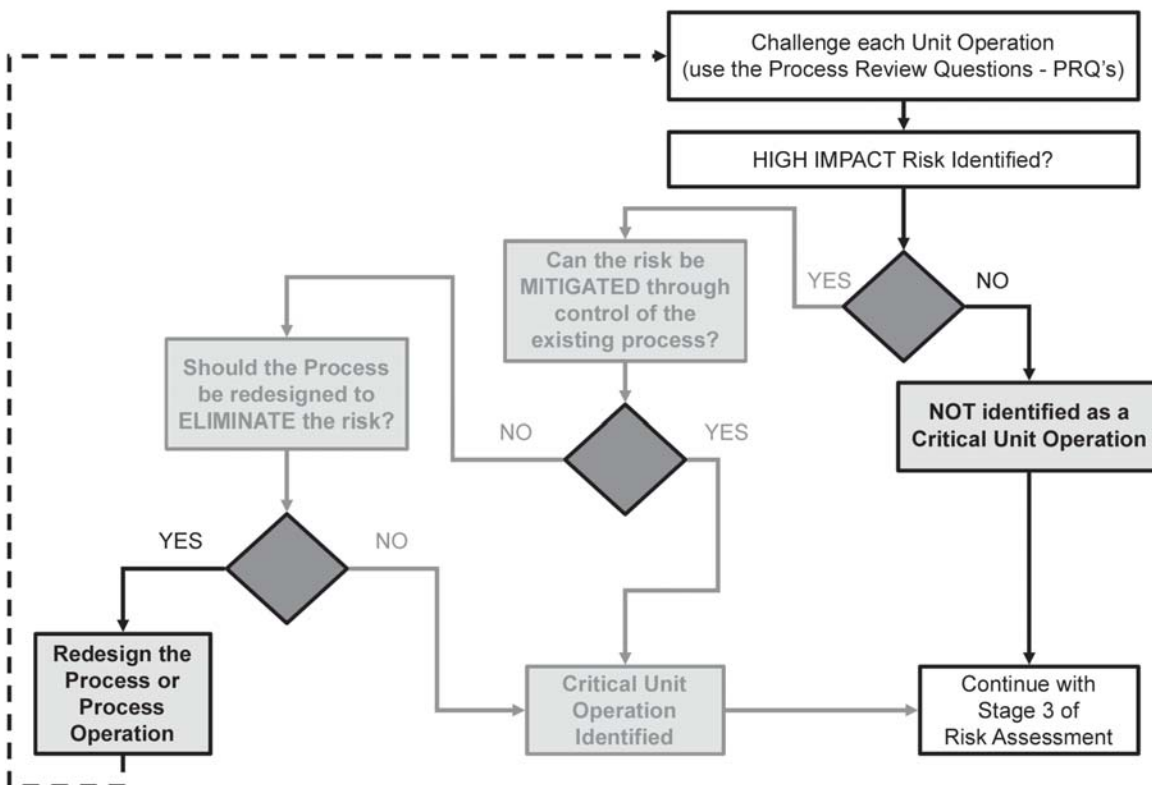
3.3.1 Stage 2 – Process Review Procedure

The aim of this stage of the Risk Assessment is to systematically review the process, unit operation by unit operation, so that the **critical unit operation(s)**, and hence, **critical process step(s)**, can be identified, i.e., a critical unit operation, by definition, can only occur within a critical process step.

The overall purpose of the Process Review (Stage 2) is to analyze the unit operations to determine the risks that the intended results will not be achieved. Figure 3.3 shows the decision flowchart, which supports the review of the risks arising from the process used to manufacture the API.

Contamination risks which may arise as a result of the internal processing environment will be reviewed in the contamination review (Stage 3 of the Risk Assessment process), e.g., compatibility of the materials with the process.

Figure 3.3: The Process Review Decision Flowchart



The procedure described in Figure 3.3 is a systematic method, which assesses risks, prompts the review team to identify means by which process risks can be mitigated and provides a way for alternative process routes to be designed and re-analyzed.

It is expected that the review team composition would be multi-disciplined.

In order to carry out this analysis, it is necessary to characterize the process from an understanding of the chemistry of the various process stages and the product, i.e., to understand the desired chemical and physical properties of the finished product.

Potential risks are reviewed during this procedure through use of the Process Review Questions (PRQs) (Table 3.1). The PRQs have been defined to identify **high risk impact** situations only occurring from one source: the process used to manufacture the API.

A “yes” answer to **any** PRQ means that a **high impact** risk has been identified and the appropriate route through the process review decision flowchart (Figure 3.3) should be followed. Upon completion, move onto Stage 3 of the Risk Assessment Process (Section 3.4).

Table 3.1: The Process Review Questions (PRQs)

Question	Typical Data (To answer the PRQ)
Is a change to the quality of the input a risk to the process? Impurities: which impurities could be introduced through the input materials? Utilities: Can utilities (e.g., water, nitrogen) generate a risk to product quality?	Input Specifications Ratio of Reactants Synthetic Chemistry Scientific Rationale (underpinning scientific knowledge) Utility Quality Control
Is there a risk to the process if the molecular form changes? Physical Form: could the wrong physical form be generated - such as an incorrect crystal form or size, or a liquid viscosity outside the desired range? Molecules: is it possible that the wrong conditions could promote side reactions or the formation of unwanted stereo chemical forms? Process Robustness: is it difficult to make the product?	
Can variation in process parameters impact on chemical and physical product quality? Impurities: which impurities could be introduced through the reaction not being carried out in the specified range of conditions? Molecules: is it possible that the wrong conditions could promote side reactions or the formation of unwanted stereo chemical forms? Process Robustness: is the process susceptible to minor variations in parameters?	Synthetic Chemistry Scientific Rationale (underpinning scientific knowledge) Risks from Process Control System
Can product quality variation go undetected? Ability to know whether it has gone wrong: if the process is not carried out in the required way, will this be undetected? End Point Determination: are reaction/crystallization end points unable to be determined?	Synthetic Chemistry Scientific Rationale (underpinning scientific knowledge)
If a process malfunction occurs at this process step, can it not be recovered by subsequent process steps (normal operation)? Forward processing: is it possible that excursions from the defined conditions could lead to an inability to advance the process to the desired end?	Synthetic Chemistry Scientific Rationale (underpinning scientific knowledge)

Example 1: In the manufacture of an API the input quality of the intermediate has the potential to impact the impurity profile of the API, i.e., a “yes” to the first PRQ. The risk is **high** and the probability remains **high** until a mitigation plan is put in place or the process redesigned. In this example, the appropriate solution is to mitigate the risk by analytical testing of the input prior to use on the API process. The input specification of the API remains a critical parameter.

Example 2: In the reaction stage of an API manufacture, the temperature can cause unwanted reactions to occur outside of a predefined range. The temperature is a critical parameter, which can be controlled within the required range.

Example 3: The manufacture of an API is difficult with the reaction requiring a precise amount of a reactant at a very specific temperature and pH within a specific level of agitation. With so many critical parameters, a cost-effective solution may be to consider re-design.

3.3.2 Determining Critical Steps and Critical Parameters

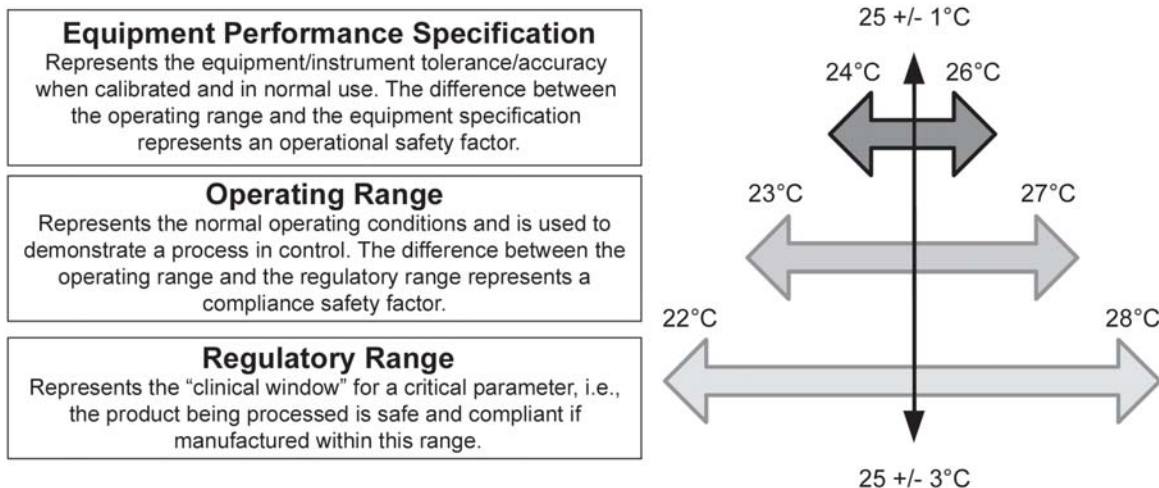
As a result of the process review, the team will be able to determine the **critical unit operation(s)**, and **critical process step(s)** that will determine whether the required final product can be made.

The facility design should then focus on those features that will enable the relevant process stages to be carried out as intended to achieve the required results.

The process review will facilitate the identification of **critical parameters** that should be maintained within predefined ranges in order to achieve the required results.

Figure 3.4 shows a typical control hierarchy, which explains the rationale for engineering the design of a system to control a **critical parameter**.

Figure 3.4: Control Hierarchy



The analysis also could contribute to a strategy for **Process Analytical Technology**, through which the critical parameters could be appropriately monitored and/or controlled to demonstrate the achievement of required properties.

3.3.3 Summary

The process review stage of the **Risk Assessment process** supports the identification of:

- critical and non-critical unit operations
- opportunities to mitigate and eliminate risk to the patient

3.4 Contamination Review

3.4.1 Stage 3 – Contamination Review

The aim of this stage of the Risk Assessment is to review systematically the process, unit operation by unit operation, so that the **Level(s) of Protection** can be defined.

The intent is to review potential risks arising from the physical contamination of the API, i.e., material not intended to be a part of the process arising from either:

The **internal** environment during “open” or “closed” processing (Figure 3.5)

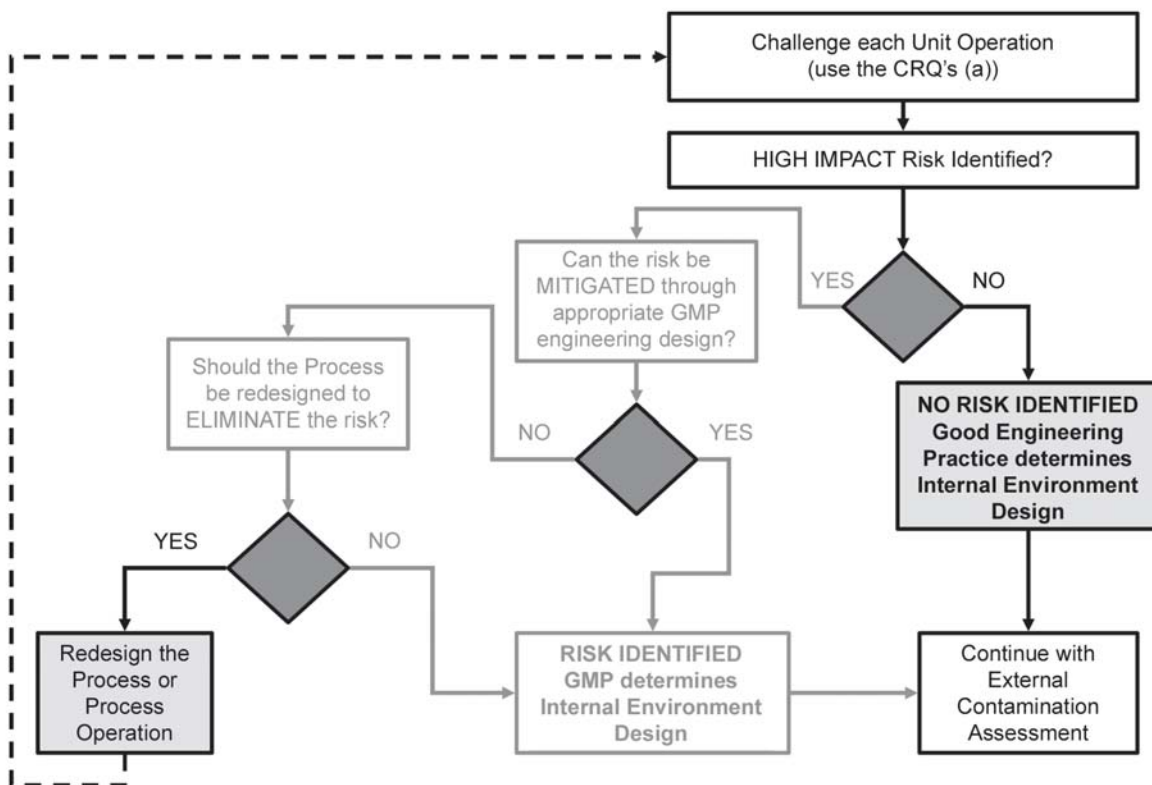
OR

The **external** environment during “open” processing (Figure 3.6)

3.4.2 Internal Contamination Review

The internal processing environment should be considered, i.e., the potential for the internal processing environment to contaminate the product (Figure 3.5):

Figure 3.5: The Contamination Review Decision Flowchart – Internal Contamination



Potential risks are reviewed during this procedure through use of the contamination review questions (CRQs) – Part (a) – (Table 3.2). The CRQs (a) have been defined to identify **high-risk impact** situations only occurring from one source: **internal physical contamination**.

A “yes” answer to **any** CRQ (a) means that a **high impact** risk has been identified and the appropriate route through the Internal contamination review decision flowchart (Figure 3.5) should be followed. Upon completion, move onto the external contamination review.

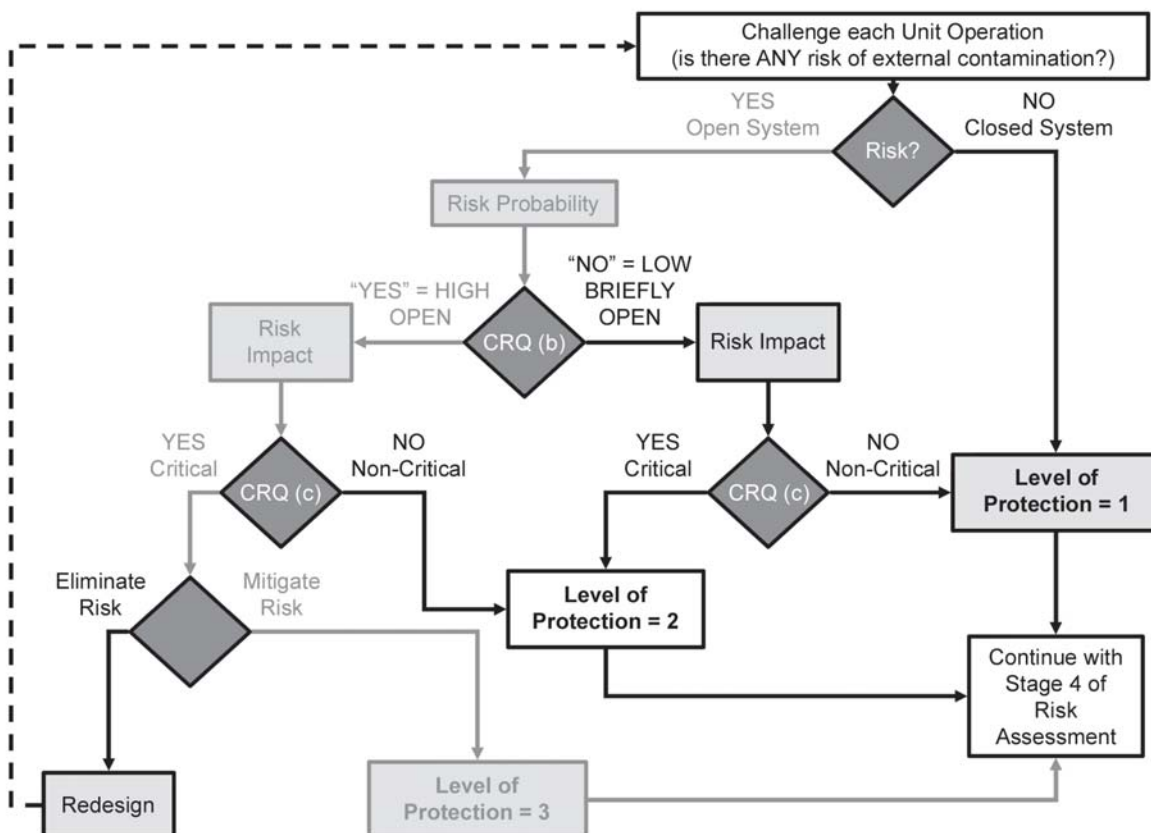
Table 3.2: The Contamination Review Questions Part (a) – Internal Contamination

Question	Typical Data (To answer the CRQ)
Can internal contamination generated from equipment impact on the product? Impurities which could be introduced by equipment Materials of Construction or Seals and Lubricants which are not compatible with the process	Synthetic Chemistry Scientific Rationale (underpinning scientific knowledge) Product Contact Materials Specification
Can internal contamination generated from cleaning impact on the product? Impurities: which impurities could be introduced through the cleaning materials or the cleaning process?	Synthetic Chemistry Scientific Rationale (underpinning scientific knowledge) Cleaning Materials Specification and Cleaning Processes

3.4.3 Stage 3 – External Contamination Review

The external environment should be considered, i.e., the potential for the external environment to contaminate the processing environment, and therefore, to contaminate the product (Figure 3.6).

Figure 3.6: The Contamination Review Decision Flowchart – External Contamination



The above approach uses a series of contamination review questions (CRQs):

- **CRQ (b)** – A series of questions to identify the risk probability (Table 3.3), i.e., a “yes” answer to **any** CRQ (b) means that a **high probability risk** has been identified and the appropriate route through the external contamination review decision flowchart (Figure 3.6) should be followed.
- **CRQ (c)** – A series of questions to identify the risk impact (critical or non-critical (Table 3.4)) so that the appropriate route through the external contamination review decision flowchart (Figure 3.6) can be followed, i.e.:
 - a “yes” answer to CRQ (c) Q3 means that a **critical risk** has been identified
 - a “yes” answer to CRQ (c) Q1 or Q2 means that there is a high probability that a **critical risk** has been identified
- Criticality here is based on the definition that **any** external contamination has the potential to adversely impact the impurity profile of the API.
- If there is a high probability of a critical risk, a review of how this could be eliminated should be undertaken, this may be by a number of different methods, e.g., engineering **or** procedural redesign.

If a risk cannot be eliminated, its impact should be mitigated, i.e., ensure the appropriate Level of Protection is in place.

Table 3.3: The Contamination Review Questions Part (b) – Identifying Risk Probability

Question	Typical Data (Required to answer the CRQ)
These questions are trying to identify when the processing is closed and when it is open . The concept of open , briefly open , and closed are meant to be applied during operation not during shutdown.	
Is the processing “open” to the external environment during normal operations? Is material charging through open man-ways on a regular basis, i.e., each batch?	Facility and Equipment Design Proposed Operating Procedures
Is the processing “open” to the external environment, for extended periods, on a regular basis for: • charging • process adjustments • sampling • other	Facility and Equipment Design Proposed Operating Procedures for Sampling, Cleaning, and Maintenance
Is the nature of the processing equipment such that external physical contamination could enter unless additional containment is in place?	Containment review, i.e., material additions, etc.