BIOTECHNOLOGY

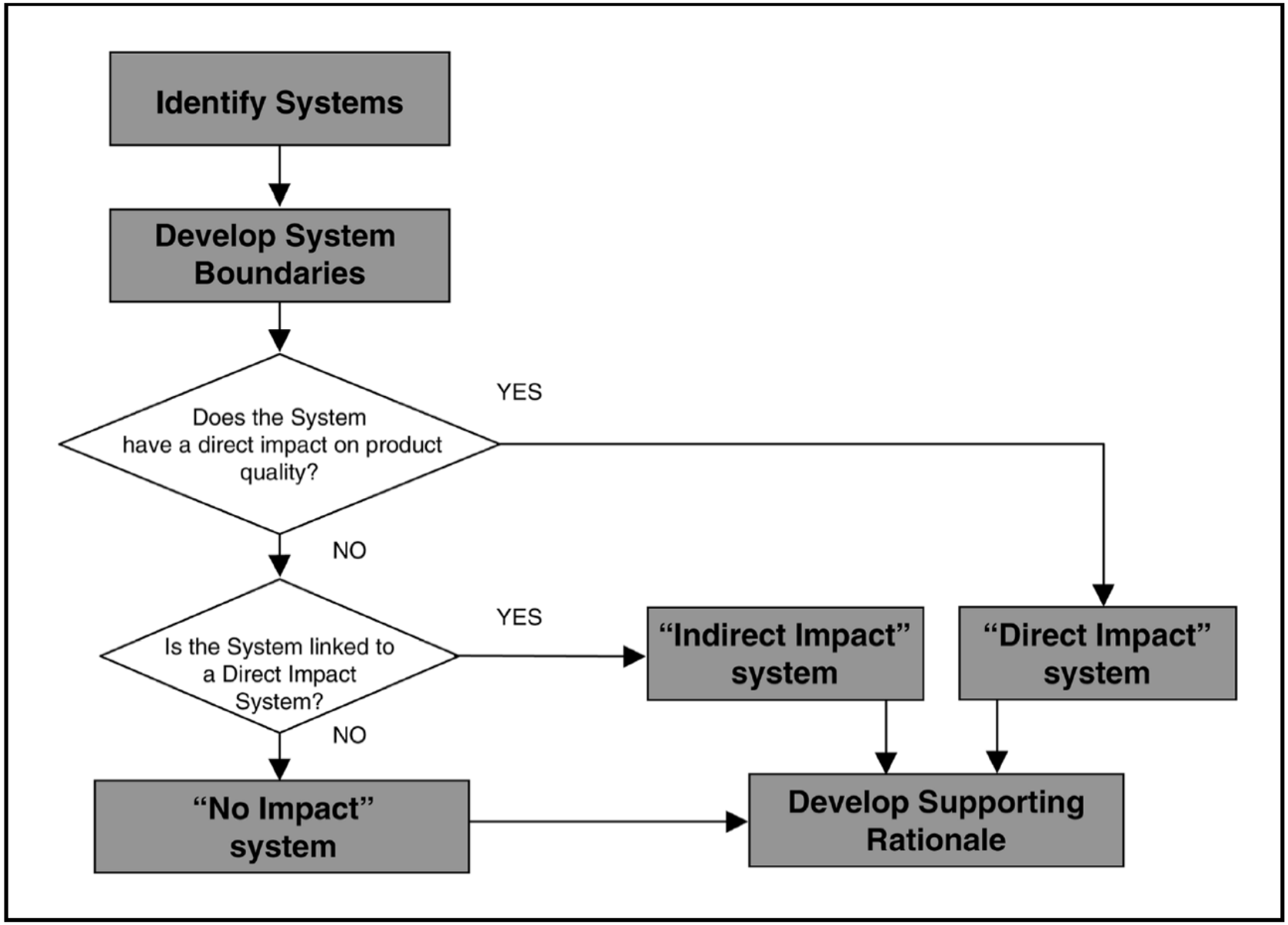
Facility design and qualification

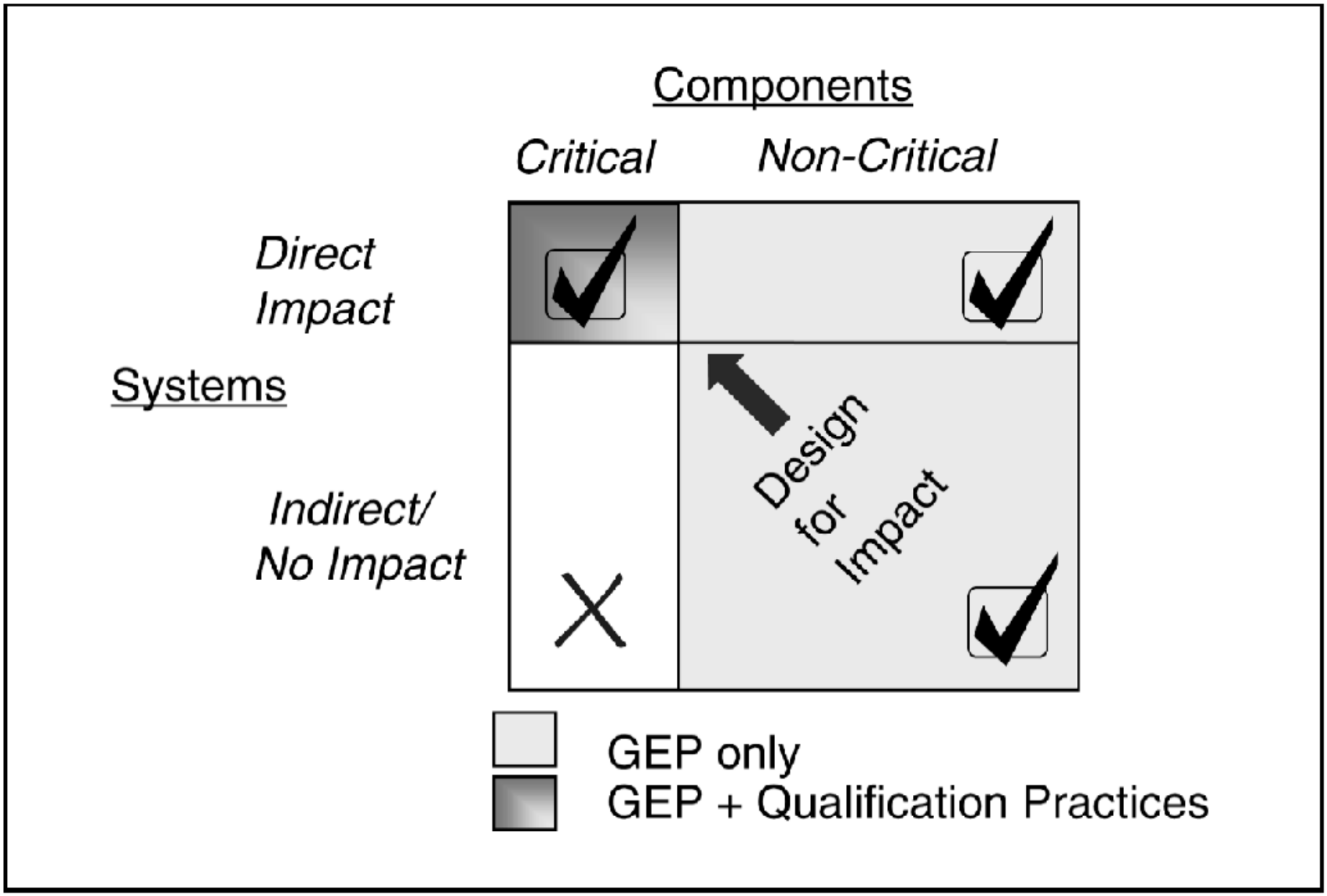
Könczöl Kálmán c. egyetemi docens

Impact assessment

Impact Assessment is the process by which the impact of a system on product quality is evaluated, and the critical components within those systems are identified.

Those systems having a direct impact on product quality are subject *to* **Qualification Practices** in addition to **Good Engineering Practice** (GEP). “Indirect Impact” or “No Impact” systems and their components are designed, installed, and commissioned according to GEP only. This process allows appropriate effort and focus to be concentrated on the quality impacting systems and components.


Identify Systems
Develop System Boundaries
Does the System have a direct impact on product quality?
YES
NO
Is the System linked to a Direct Impact System?
YES
NO
"Indirect Impact" system
"Direct Impact" system
"No Impact" system
Develop Supporting Rationale


Components
Critical
Non-Critical
Direct Impact
Systems
Indirect/ No Impact
Design for Impact
GEP only
GEP + Qualification Practices

Design for impact

"Design for Impact" is used to describe the practice of making conscious design decisions with respect to the impact of a system **at the beginning of design development.** There are many systems in a typical project, and the impact of each of these systems will be determined by their design and application. By careful design, the number of systems capable of having a direct impact can be reduced. The direct impact **functions** remain but are logically incorporated into the most appropriate systems by the designer to preclude excessive and unnecessary qualification and validation work later on.

It is suggested that a preliminary System Impact Assessment be made early in the project, between system definition and equipment ordering. Component criticality assessment should be performed once the detailed design is sufficiently developed to do so. Following the assessment of component criticality, the impact status of each system can then be confirmed.

Impact Assessment should be integrated into the project schedule. The effort required will correspond with the complexity of the systems and the processes involved, and it is important that sufficient time is allowed within the schedule.

Good Engineering Practice (GEP)

"Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate cost-effective solutions."

As such, GEP is comprised of the following:

- Professional and competent project management (processes, procedures, and staff)
- Professional and competent engineering design, procurement, construction, and commissioning
- Full consideration of applicable safety, health, and environmental statutory requirements
- Full consideration of operation and maintenance requirements
- Full consideration of recognized industry standards and guidance
- Appropriate documentation for ongoing operation and maintenance, and to demonstrate compliance with applicable regulations and codes

Documentation

Good Engineering Practice recommends that:

- Each component should be built in accordance with plans and specifications, approved or authorized by the appropriate individuals
- Each component should be inspected, tested, and documented by qualified individuals
- A minimum level of documentation should be provided for all systems and equipment
- Documentation should cover design, fabrication, construction, inspection, and commissioning

Engineering firms, suppliers, contractors, and owners provide the documentation necessary for design, construction, commissioning, qualification, operation, and technical support of the facility, utilities, equipment, and other systems. A clear understanding of these documents maximizes their value and eliminates redundancy.

If these documents are appropriately planned, created, organized, and authorized, they may become an integral part of the qualification support documentation for "Direct Impact" systems.

This Guide recommends that a document matrix is established to encompass:

- All of the documents that are to be prepared or collected throughout the project
- The required timing
- Who is responsible for preparation (or collection), review and approval, and in what capacity the approval is made

User requirements

Project Purpose and Justification

Existing background information and the rationale for the project request should be communicated. Items that may be included are:

- Statement of existing conditions
- Project justification (e.g., new product(s), increased demand, problem remediation, cost savings, process improvement)

User requirements

Product and/or Process Requirements

A list of affected products and associated details provide the fundamental basis for the scope development. Much of this information may be obtained from development reports, technical reports, batch records, regulatory submissions, sales/marketing data, and staff input. Information to be considered includes:

- Product forecasts (and ranges)
- Potential or restrictive batch sizes or ranges
- Process descriptions, flow charts, and estimated processing times
- Known operating ranges and tolerances for critical process parameters
- Known operating restrictions or difficulties

- Safety information for the associated materials and processes
- Known compatibility or incompatibility for materials of construction (including seals)
- Cleaning methods, agents, and limits
- Past experience with current products or current processes
- Past experience with similar products or similar processes
- Preferred equipment suppliers (and basis for preferences)
- Site-specific requirements (e.g., local suppliers, spare parts)

Allowable operating ranges and limits (or tolerances) provide the basis for future design, commissioning, and qualification requirements. Operating limits are defined as the minimum and/or maximum values that will ensure that product and safety requirements are met. Appropriate values must be provided to ensure that meaningful set points, alert values, and alarm values can be established, thus eliminating potential nuisance alarms.

User requirements

Operational Considerations

Operational considerations should be communicated to ensure that the user intent, and the flexibility and/or constraints, are understood. Items to consider include:

- Planned or expected plant operating schedule (e.g., one shift x five days, three shifts x five days, three shifts x seven days)
- Planned staffing for new or renovated facility/area (e.g., use existing staff, hire new staff)
- Potential or allowable disruption of existing operations (especially in cases of renovation or plant expansion)
- Potential or allowable impact on existing operations (especially in cases of renovation or plant expansion)

Maintenance and technical support requirements

Staff responsible for facility (and utility system) operation, utility system and equipment maintenance, and technical support (e.g., plant and process engineering) offer a different perspective than the End-User. Key support staff should be consulted at this stage to incorporate their requirements, and possible constraints, into the scope document. Information to be considered includes:

- Past experience with products, processes, equipment, and systems
- Preferred equipment suppliers (and basis for preferences)
- Site-specific requirements (e.g., local suppliers, spare parts, internal standards)

Compliance requirements

It is important that external compliance requirements (especially those for cGMP, safety, or environment) are clearly communicated. Particular emphasis is warranted where there are newly formed regulatory requirements, or local requirements, that differ from FDA requirements. The project team should consult with QA on project-specific compliance requirements.

Deliverables

This phase typically yields the following key deliverables:

- A final User Requirements Brief
- A Requirement Specification for each system
- A Project Execution Plan

User Requirements Brief

At the completion of this phase, it is recommended that a final User Requirements Brief is prepared and appropriately authorized by key stakeholders. This document will provide a basis for the development of future project documentation, including the Requirement Specifications for individual systems.

Requirement Specification(s)

These are a detailed documents used to specify the requirements of the user for individual aspects of the facility, item of equipment, utility, and systems in terms of function, throughput, operability, and applicable local standards. Each of these documents should be appropriately authorized by key stakeholders.

Both the User Requirements Brief and Requirement Specifications should be subject to change control during their development, with involvement from the appropriate stakeholders.

Project Execution Plan

A written plan is an effective means for the project manager to communicate to the user and other stakeholders, the approach to be taken for project execution. A plan should be developed with input from the project team as early as is practical.

The following topic areas may be considered for discussion within the plan:

- Project purpose, scope, and key business objectives
- Expected milestones and timing
- Funding strategy and budget status
- Resource strategy (for design, construction, and commissioning)
- Strategy for control of schedule, cost, quality, and scope
- Strategy for management and control of documentation
- Impact on existing operations, including required shutdowns or accommodation of existing operations
- Project leadership, stakeholders, and project team representation
- Supplier selection criteria and process

Conceptual Design

The conceptual design stage is used, where necessary, to generate various alternatives for evaluation in response to the demands of the final User Requirements Brief and the Requirement Specifications for individual systems. The project team selects the concepts to be taken forward into the functional design stage.

Detail Design

The detail design stage produces the documents required for construction bidding and contracting, system and equipment purchase, fabrication, installation, and testing.

Piping and Instrumentation Diagrams

P&IDs serve as the primary source of design information for utility systems and process equipment. They are used to depict the process flow, equipment configuration, process parameters, instrumentation, and materials of construction. They also are used to perform overall material and energy balances along with pressure balances. The following guidelines are recommended to obtain the maximum benefit from these drawings:

- Indicate entering/leaving support services and process streams; include reference to appropriate drawing and/or sheet number
- Identify system boundaries, with respect to support services and entering/leaving process streams
- Identify the battery limits of skid-mounted (or packaged) equipment
- Identify all components with appropriate tag numbers, using nomenclature consistent with existing plant practices. This eliminates the need for re-numbering or cross-reference listings.
- Indicate line number, service, line size, and direction of flow for all piping and tubing
- Indicate material type and insulation type/thickness (if applicable) for all pipe lines
- Indicate use (purpose), size, capacity, material type, and insulation type/thickness (if applicable) for all equipment (e.g., tanks, pumps, heat exchangers)
- Indicate size, type, and material type of all valves
- Provide material and energy balance information for each line number

Good Engineering Practice suggests that these documents be kept up to date throughout the project and the life of the facility or system.

Commissioning

”A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations.”

Commissioning stakeholders

System Impact	Stakeholder Group
Direct	Engineering, Manufacturing, Quality Assurance, Validation, Contracting, Supply
Indirect	Engineering, Manufacturing, Supply, Contracting
None	Engineering, Manufacturing, Supply, Contracting

Commissioning deliverables matrix

Legend: W = Write and maintain R = Review A = Approve E = Execute	Commissioning Leader	QA/Validation*	System Owner (Operational End User)	Project Engineer	Contractor(s)/Suppliers
Commissioning Plan	W&E	R	R	A	-
Commissioning Schedule	W	R	R	A	-
Commissioning Budget	W	R	R	A	-
Overall Test Plan	W&E	R	R	A	-
Pre-delivery Inspection (PDI) Plan	R	A	A	W	W&E
Pre-delivery Inspection (PDI) Report	R	A	A	W	W
Factory Acceptance Test (FAT) Plan	R	A	A	W	W&E
Factory Acceptance Test (FAT) Report	R	A	A	W	W
Inspection Plan	R	A	A	W	W&E
Inspection Report	R	A	A	W	W
Functional Test Plan	R	A	A	W	W&E
Functional Test Report	R	A	A	W	W
System Test Summary Report(s)	A	A	A	W	-
Final Commissioning Summary Report	W	A	A	A	-
*"Direct Impact" systems only					

Functional (or Basic) Design

The functional design stage generates the key design documents, which are used as a framework for the detailed design process. These documents include:

- Site plans
- Floor plans
- Process and Material flow diagrams
- Air flow diagrams and HVAC schedules
- Electrical one-line diagrams

A sequence of operations is prepared for each system. It provides a detailed description of:

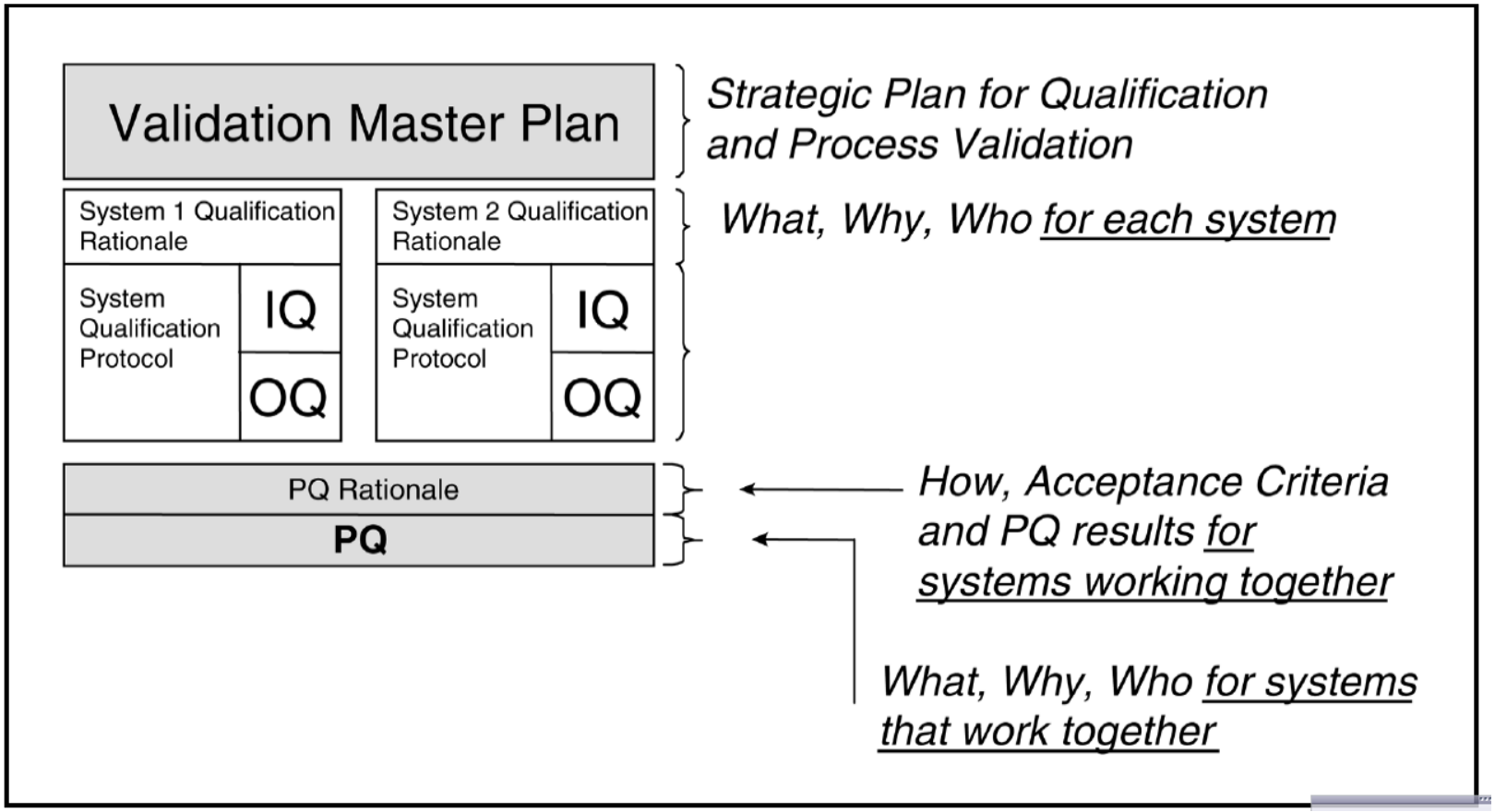
- System Start-Up
- Normal operation and cleaning (as applicable)
- Process monitoring
- Data acquisition and Archive
- Alarm conditions and response
- Shut-Down

Validation Master Plan (VMP)

As a guidance document, the VMP should outline the overall validation philosophy and approach to be used through the life of the project. This outline should:

- Include the strategy to be used for qualification and commissioning of the facility
- Position the impact assessment process, Good Engineering Practice, and Qualification
- Outline the relationship and interdependency of the qualification activity with the commissioning activity

The VMP is the key document that governs the testing and documentation required to satisfy the regulatory authorities. This document also brings structure to the verification of installation and operational testing. Ideally, this document is generated and approved during the planning stages, prior to commissioning and qualification, of the project.


Validation Master Plan
Strategic Plan for Qualification and Process Validation
System 1 Qualification Rationale
System Qualification Protocol
IQ
OQ
System 2 Qualification Rationale
System Qualification Protocol
IQ
OQ
What, Why, Who for each system
PQ Rationale
PQ
How, Acceptance Criteria and PQ results for systems working together
What, Why, Who for systems that work together

Enhanced Design Review (EDR) is the term adopted by this Guide to describe the process by which engineering designs for pharmaceutical facilities, systems, and equipment are evaluated. This process compliments **Good Engineering Practice.**

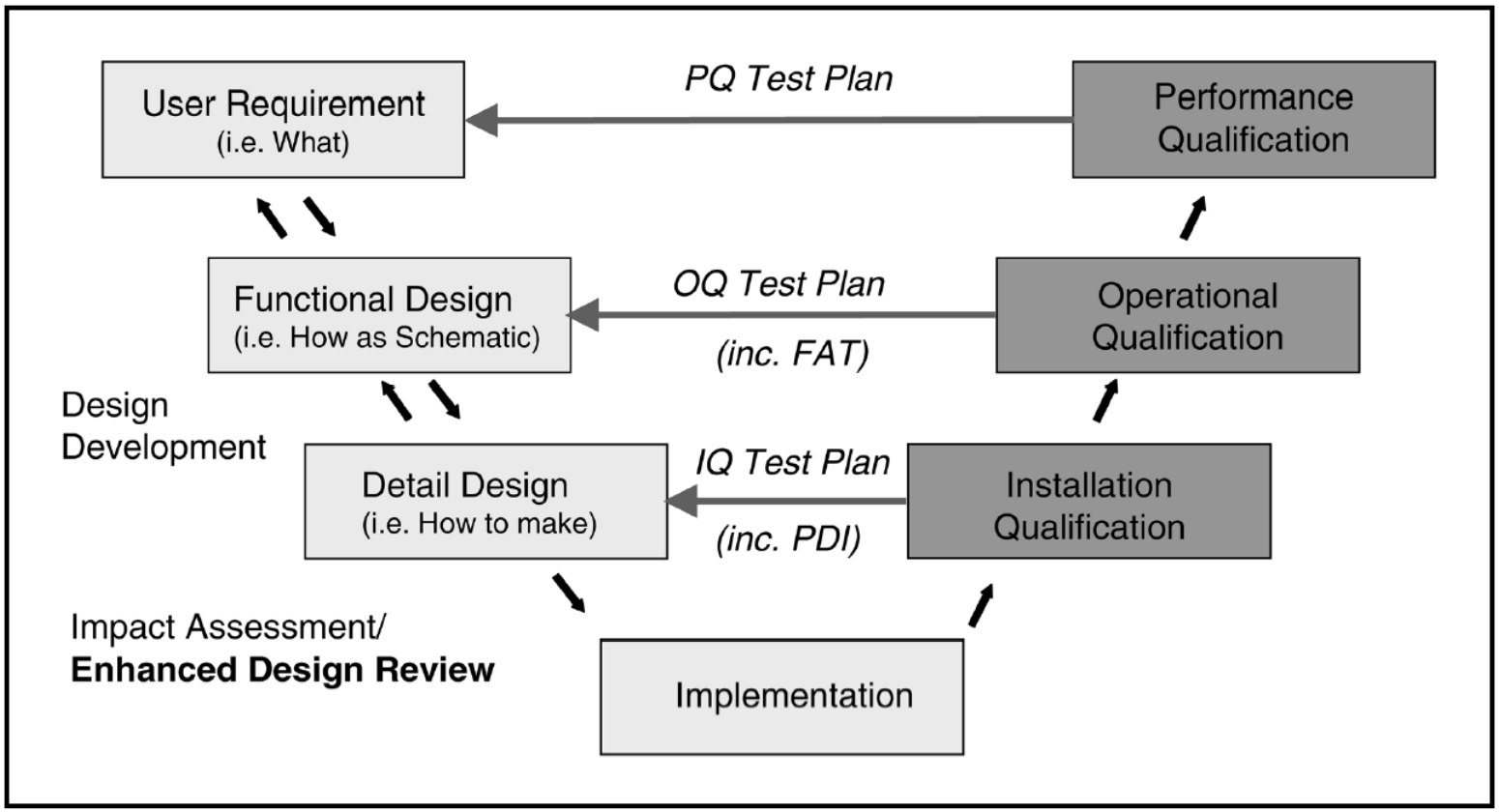
EDR is defined as:

"A documented review of the design, at an appropriate stage in the project, for conformance to operational and regulatory expectations."

EDR may be used as a tool to provide a structured assessment of the design of facilities, utilities, and equipment. This should assure the regulatory authorities that the design process has been carried out in a controlled manner and that an audit trail exists from conception of the project up to the completion of the detailed design.

Factory Acceptance Tests (FAT)

Whenever appropriate, static and/or dynamic testing to support the qualification efforts should be conducted and documented at the supplier site. Supplier site testing will allow for troubleshooting and problem resolution of the system prior to shipment, providing for a higher level of assurance that the system will meet specifications and function properly upon delivery. Supplier site testing should be performed with the End-Users so the system can be challenged to best simulate actual production conditions.


User Requirement
(i.e. What)
PQ Test Plan
Performance Qualification
Functional Design
(i.e. How as Schematic)
OQ Test Plan
(inc. FAT)
Operational Qualification
Design Development
Detail Design
(i.e. How to make)
IQ Test Plan
(inc. PDI)
Installation Qualification
Impact Assessment/
Enhanced Design Review
Implementation

Installation Qualification (IQ)

"The documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g., construction, materials) and are correctly installed."

Only "Direct Impact" systems will be subject to IQ. Installation Qualification is subject to QA approval and any change subsequent to this stage requires QA review and approval.

Examples of commissioning integration with IQ include:

1) The P&ID of a system can be verified during the "Physical Completion" and Inspection phase of commissioning. If this activity has been performed following qualification practices, the exercise will not have to be repeated in the IQ phase.

2) Instruments and equipment can be verified (manufacture, model number, materials of construction, etc.) at the supplier's site during a Pre-Delivery Inspection (PDI) or Factory Acceptance Testing (FAT). If these items are not altered or dismantled in any way for transport, these checks, if properly documented, could be used in support of qualification activities, and would not have to be repeated.

Sufficient engineering information and documentation should be available to write the IQ protocol. If engineering documents are appropriately planned, created, organized, and authorized, they can be an integral part of the qualification support documentation for "Direct Impact" systems. The following is a list of documentation, per system, that is typically required to write an IQ protocol:

a) Validation Master Plan (VMP)

b) User Requirements Brief and Requirement Specification

c) Supplier Drawings and Specifications, including:

- Purchase Orders and Contracts
- Manufacturer's Data Sheets
- Process Description
- P&IDs
- Equipment List
- System Hardware/Software Specifications
- Instrument List

Operational Qualification (OQ)

"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality operate as intended throughout all anticipated ranges."

Only "Direct Impact" systems will be subject to OQ. Operational Qualification is subject to QA approval and any change subsequent to this stage requires QA review and approval.

The OQ is performed on systems, which may consist of facilities, utilities, and/or equipment; to verify operation within specified parameters, such as temperature, pressure, flow, etc. Execution of the OQ involves testing parameters that regulate the process or product quality. Verification of proper operation of controllers, indicators, recorders, alarms, and interlocks, is performed and documented during the OQ testing.

If Factory Acceptance Testing (FAT) is executed for the equipment, some or all of these tests can be performed at the supplier's site. If the system is a distribution system, or another type of system, which can only be assembled on site, these tests can be performed as part of the commissioning activities. The tests that could not be performed prior to this point in time, for critical components of "Direct Impact" systems, are then performed as part of the Operation Qualification.

Sufficient engineering information and documentation should be available to write the OQ protocol. If engineering documents are appropriately planned, created, organized, and authorized, they can be an integral part of the qualification support documentation for "Direct Impact" systems. The following is a list of documentation that is typically required to write an OQ protocol:

a) P&IDs

b) Functional Requirement Specification

c) Equipment operations manuals

d) Standard operating procedures

e) Supplier Drawings and Specifications, including:

- Process Description
- Equipment List
- Instrument List
- Alarm/Interlock schedule
- Control system operation manuals
- References for local, national, and international codes and standards

Performance Qualification

"The documented verification that all aspects of a facility, utility, or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria."

Only "Direct Impact" systems or a combination thereof, will be subject to Performance Qualification. Performance Qualification is subject to QA approval. As with the IQ and OQ phases, changes subsequent to the PQ stage require QA review and approval.

Performance Qualification must not be confused with Process Validation (PV) (or qualification that is the verification that good product is made), or with validated cleaning and analytical methods; these are beyond the scope of this Guide.


BIOTECHNOLOGY
THANK YOU FOR YOUR ATTENTION!