This article discusses some of the challenges, execution methods, and potential opportunities of Design Qualification (DQ).

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Do You DQ? Design Qualification Challenges and Considerations

by Allan MacDonald

Why DQ?

The regulatory authorities of the European Union, Japan, and the United States have come together to form the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). ICH Q7A was the first Good Manufacturing Practice (GMP) guidance developed jointly by industry and regulators under the ICH umbrella. The document establishes one global GMP standard for Active Pharmaceutical Ingredients (APIs).

Following suit, the US Food and Drug Administration (FDA) has stated, "Q7A supersedes FDA's draft API guidance."[1] The ICH Q7A guidance defines DQ as "the documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose." This definition for DQ is the same as the one found in the Commission of the European Communities Guide for GMP.[2] This European Union (EU) document also states, "the first element of the validation of new facilities, systems, or equipment could be design qualification."

The requirement for DQ can be debated since the above-mentioned documents use words like "could," "should," and "usually," and because these are guidance documents only, not regulations. However, government guidance documents *usually* carry a lot of weight in a historically "risk-averse" environment like the pharmaceutical industry. Therefore, many companies are implementing DQ programs and procedures and are expecting others to support these efforts.

Definition Before Qualification

To verify that a proposed design meets the intended purpose, we are required to understand each of these terms. The challenge is that both the definition of the "purpose" and "design" evolve during the life of a project. So there is a temporal component to DQ that must be addressed. The pharmaceutical manufacturer should decide early in the project when a DQ will be executed.

The EU GMP and ICH Q7A both use the term "proposed design" in their DQ definition; however, this only reflects the status of a design at the time the DQ was performed. For a DQ to be valid, the Installation, Operational, and Performance Qualification (IQ, OQ, and PQ) each must be performed on the system or equipment that was constructed per the design that was qualified.

At a minimum, a DQ needs to be performed on the final design. But, from a project standpoint, waiting until the design is final before verifying that it meets the intended purpose is not practical. Rather, verifying the design along the way will allow for design corrections to be made with minimal impact on cost and schedule. Whether or not this verification is documented and included as part of DQ is up to the owner of the system or equipment to be qualified. However, documenting earlier efforts can reduce the effort required for the DQ on the final design.

A design can be defined by documents such as:

- Descriptions (Process, Basis of Design)
- Specifications (User Requirement, Functional, Design)
- Drawings (Process Flow Diagrams (PFD), Piping and Instrumentation Diagram (P&ID), Layout)
- Purchase Orders
- Contracts

Specification Resource

There is a group in ISPE that focuses on GAMP in the Americas. A subgroup of that group was formed called the Joint Equipment Transition Team or JETT.

The group defines themselves on the JETT homepage at http://www.jettconsortium.com as the following. "JETT is a consortium of pharmaceutical users (manufacturers), equipment suppliers, and consultants seeking to improve communications between users and suppliers to more effectively meet the 'validation' requirements of the pharmaceutical industry."

This consortium has produced URS templates for various pieces of equipment that are available for download free of charge from the site. These templates have been created based on the GAMP 4 methodologies.

In addition to the many URS templates available, sample design and functional specification are included on the site.

A matrix on the sample documents Web page provides the status of current and future documents the JETT is working on.

For the execution of the DQ to be efficient, the user and designer need to define – in advance – the path a design will take for each type of equipment. The Code of Federal Regulations (CFR) requires manufacturers of medical devices to keep a Design History File (DHF).[3] Although this is not required for pharmaceuticals, a DHF could be used as part of a DQ. The user, designer, and validation group could agree on the types of documents to be in the DHF for the equipment or system that they will be designing. These documents are generated and copies should be collected during the design process.

Some of the documents in the DHF might be:

- the original user request
- emails and minutes from meetings and teleconferences
- calculations
- PFDs and P&IDs
- drawings

The items referenced in the DHF would be used to verify your design in a DQ.

Specifications

Specifications are an important part of what defines the design of a system or piece of equipment. Companies within the pharmaceutical industry frequently use common terms for specifications that unfortunately may have different meanings, interpretations, and impacts.

For example, the User Requirement Specification (URS) as described in GAMP 4 is to be used for describing what a system is supposed to do.[4] This entire guide was written for use with automated systems; however, the term URS is often being used broadly to include many, if not all, specifications being produced by the user or their designee. This can often be confusing once validation groups attempt to use the now classic "V-model" and arrange their PQ to verify all items in a URS.

GAMP 4 states in a section describing the URS that "a separate requirements specification should provide appropriate production process and product information, electrical and mechanical details, and performance requirements."[5]

It is also common for a firm to design a control system for a client and create a specification for bid that not only has the user's requirements, but also some functional and design specifications. This is so the proposals or bids received from potential suppliers can be tabulated and compared on an "apples to apples" basis.

Once a successful bidder is awarded the project, they then go on to create a complete Functional Specification (FS) and Design Specification (DS). In this case, what would the specification that was sent out for bid be called? It is more than a URS and it has elements of an FS and a DS. To minimize confusion on a project, the terms and accompanying definitions that will be used by all parties on a project should be identified. Check for instances that those involved not only all know what a URS is, but also agree on the same definition and where it will be applied.

Agreement in advance on what pieces of design will have a URS, FS, and DS and which ones will have another type of specification is an important step in the process.

Portions of the facilities, systems, and equipment that will undergo DQ may be specified using methods common in the construction trade such as those advocated by the Construction Specifications Institute (CSI). Mechanical, Electrical, Plumbing (MEP), Heating, Ventilation, and Air Conditioning (HVAC), and architectural building contracts are often specified using different methods than process system equipment or control systems. These differences should be addressed in advance so that all parties involved in the design and qualification of that design have the same expectations. The DQ procedures and forms also should allow for the use of construction contracts and documents.

Design Qualification vs. Enhanced Design Review

The ISPE Baseline® Guide Volume 5 "Commissioning and Qualification" has adopted the term Enhanced Design Review (EDR).[6] EDR is a practice that the guide suggests to utilize to compliment Good Engineering Practices (GEP). As defined, an EDR is a documented review of the design, not necessarily limited to systems to be qualified and not a requirement of the FDA. This author highly recommends reading the material covered in the ISPE Commissioning and Qualification Baseline® Guide.

Although the ISPE Guide avoids the term "Design Qualification," the methods described for an EDR could be used as a DQ. Many firms, particularly those involved with international business, are developing or have developed DQ proce-

dures. At a minimum, when a documented design review is performed on systems or components that are to be qualified, the review should be performed as a DQ.

Validation Plan

A validation plan is needed early in the project to determine how facilities, systems, and equipment will be validated. The validation plan should be shared with the project team, particularly with those that will be performing the design.

The validation plan should address an impact assessment and qualification rationale.[7] The plan determines what will be qualified; part of this qualification may be DQ. For example, the plan may state that "all elements of a design that have been determined to have a potential to impact product quality shall be qualified during a DQ."

If applicable, the intent to perform DQs on a project should be decided before a Request for Proposal (RFP) goes out for bid to design firms.

DQ Execution

The pharmaceutical manufacturer or their designee must provide a specific document that defines the user's requirements to meet the intended purpose of the system or equipment. The team needed to verify a design must understand the intended purpose and have the appropriate background to evaluate the proposed design. The DQ team may include:

- System User
- Designer of the System
- Validation
- Quality Assurance
- Project Management

DQ team members should have access in advance to the information that will be presented and evaluated during that DQ execution. Each team member also should know in advance what will be expected of them and what procedures will be followed during the execution of the DQ.

Each user requirement should be listed or referenced specifically in the DQ document. During a DQ, the design elements that meet each specific requirement in that user document should be verified, and each of the design documents being verified should be uniquely identified.

The history of a design should be known and available as a DQ is performed. The evolution of a design usually involves meetings, calculations, and correspondences that should all

XYZ Inc.

User Requirement

Project Name: Yitsnotadrugatol Large Scale Production Facility

Doc.No.: URD-123589-4 **Rev:** A
Project # 123589
Location: Anywhere, CA

System Description: Cyclization Reactor

Page ___ **of** ___
Date: Jul/06/2004

Requirement Number	Requirement Description	May Impact Product Quality	Requirement Category
URD-23859-4-1	Cyclization Reactor to have sufficient volume for the conversion of 400 kg (880 lbs) of intermediate in a single batch.	Yes	Process
URD-23859-4-2	All wetted materials of construction to be compatible with the chemicals to be used in the reactor.	Yes	Process
URD-23859-4-3	Reactor transfer pump to be able to pump entire contents to the quench tank in the isolation room in less than 15 minutes.	Yes	Process
URD-23859-4-4	All electrical equipment on the reactor to be rated for a Class 1 Div1 Group C, D.	Not Directly	EH&S
URD-23859-4-5	Reactor Manway to have lift assist.	No	EH&S

Notes:

Created By:

K. D. Davis	*Kevin Davis*	*Operations Manager*	*Jul/12/2004*
Signature	Name (Print)	Title	Date

Reviewed By:

B. Strichter	*Beatrice Stricter*	*Validation Manager*	*Jul/12/2004*
Signature	Name (Print)	Title	Date

Please note that the above is an example of a single page of a document that would include sections for information such as titles, document approvals, procedural references and places for the identification of signatures and initials.

Figure 1. Example of a user requirement document.

XYZ Inc.

Project Name: Yitsnotadrugatol Large Scale Production Facility

Design Qualification
Doc.No.: DQ-123589-4
Project # 123589
Location: Anywhere, CA

Design Requirements to be Verified: Cyclization Reactor system requirements as described in URD-123589-4, Rev: A., Jul/06/2004
Note: This DQ is limited to the requirements of the design that could have a direct impact on product quality. (See attached copy of URD)

Page ___ **of**
Date: Oct/15/2004

Design Documents Verified (Include Revision/Date)	Design Verification Description	Pass/Fail	Verified By/Date
D1- 12539 Rev 0 (Jul/28/2004) D2- 12539 Rev 0 (Aug/30/2004)	The Design Basis and Process Description represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-1, URD-23859-4-2, and URD-23859-4-3.	PASS	AJM Oct/22/2004
PID-123589-4 Rev 0 (Aug/30/2004) PID-123589-5 Rev 0 (Aug/30/2004)	P&IDs represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-3.	PASS	AJM Oct/22/2004
EA-123589-104 Rev 0 (Sept/01/2004) P-123589-104 Rev 0 (Sept/01/2004) P-123589-105 Rev 0 (Sept/01/2004) P-123589-106 Rev 0 (Sept/01/2004)	Equipment Arrangement and Piping drawings are consistent with the P&IDs and represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-3.	PASS	AJM Oct/24/2004
SPE-12539-18111 Rev 1 (Sept/10/2004) SPE-12539-18222 Rev 1 (Sept/15/2004)	Engineering Purchase specifications for the Pump P-401 and the reactor R-401 represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-1, URD-23859-4-2, and URD-23859-4-3.	PASS	AJM Oct/22/2004

Design History Documents: (The documents listed below were used in the verification of the design documents above.)

XYZ Meeting Minutes No. 52 (Aug/10/2004), pump and system pressure calculations by J. Smith, Aug/25/2004.

Comments:

Per meeting minutes No. 52, the quench tank T-402 will now be located in the same room as the reactor. The design team agreed that the intent of requirement URD-23859-4-3 was that the quench took place in under 15 minutes to avoid excessive reaction by products. The calculated transfer rate and equipment specifications of the design were consistent with this requirement and therefore the Equipment Arrangement and Piping drawings were verified as meeting the requirement.

Reviewed By:

B. Strichter	*Beatrice Stricter*	*Validation Manager*	*Oct/30/2004*
Signature	Name (Print)	Title	Date
K. D. Davis	*Kevin Davis*	*Operations Manager*	*Oct/30/2004*
Signature	Name (Print)	Title	Date

Figure 2. Example of a design qualification form.

be documented and indexed so pertinent points can be specifically referenced.

The correspondences, calculations, and other supporting documents also should be created with unique references. These references will help in following the path of the design during a design qualification.

Systems can be used to track a design as it evolves through the use of a traceability matrix similar in concept to that described in GAMP 4.[8] This, however, may not be appropriate for designs that are unlike the control systems that lend themselves well to a tabular representation, such as a matrix.

The form, protocol, or document completed for a DQ should provide sufficient information to identify all of the documents used to verify the design. A method should be put in place in advance for maintaining documents to be used for review/DQ by those responsible for the design.

Strict change control involving user validation personnel needs to be instituted once a DQ process has begun on a given system. This is to ensure that the design documents remain in a qualified state.

Deviations or additional requirements that arise in meetings or in correspondences that were not in the initial user's requirements or scope should be explained in the DQ document. Changes also should be submitted to the appropriate party to update the user's requirement or scope document.

The timing of the execution of a DQ is important to the schedule of a project. The final DQ on a system should be late enough so that all of the design documents have been completed, but early enough so that the fabrication or construction is not delayed. Project management should be aware that any fabrication or construction on a system that is to be qualified would be "at risk" if performed before a DQ had been completed on the proposed design.

Sample Project with DQ

A pharmaceutical company (XYZ Inc.) has hired an engineering firm to design a large scale manufacturing system for their new product that they currently make on a smaller scale.

XYZ Inc.'s goals for the project were spelled out in an RFP for a conceptual study. A conceptual study was performed by a design firm with several options and an accompanying rough estimate for the different options. Project options were chosen and preliminary engineering began.

A preliminary design with drawings (PFDs, P&IDs, lay-

outs, etc.) and a ±20% estimate was developed for capital cost approval. The estimate exceeded what XYZ Inc. had expected the cost to be. A "value engineering" exercise was then performed to reduce the scope and cost of the project. Once the estimate was within XYZ Inc.'s budgeted amount, the early design documents were revised to reflect the value-engineered scope of the project.

The documents were then used by XYZ Inc. to group portions of the project into systems. XYZ Inc.'s Quality Assurance group then had a Validation Master Plan (VMP) created. The VMP had a list of systems and whether they were to be considered a direct impact system. The VMP also stated that a DQ would be carried out on direct impact design elements only.

XYZ Inc. uses a document they call a User Requirement Document (URD) to convey their needs for the project. The document also designates which of those needs their process operations and validation groups feel could have an impact on the quality of the product on direct impact systems.

XYZ Inc.'s VMP states that a DQ will be performed on direct impact systems and equipment before design documents are approved for fabrication or issued for construction.

Once a direct impact system has successfully passed a DQ, the design documents for that system can be approved for fabrication or issued for construction. These same documents then become controlled documents under XYZ Inc.'s Quality Assurance program. Updates or revisions to these documents then require a QA/Validation evaluation as to whether they constitute a change to the executed DQ.

XYZ Inc. had required a DQ before construction of each design; however, the team would also be required to perform a design review at regular intervals during design to check that URD points for all systems are being met by the design.

The design team members were sent copies of the User Requirements document, URD-123589-4 Rev. A, that had been written earlier in the project in advance of the time set for the DQ of the Cyclization Reactor. See Figure 1 for an example page of the URD-123589-4 Rev. A document. A list of the design and design history documents that would be used in the DQ was also sent to the disciplines responsible for the documents.

During the execution of the DQ, the team members examined each of the design documents listed on DQ-123589-4 (Figure 2) and verified that the design documents will meet the requirements that may have an impact on product quality as listed in URD-123589-4 Rev. A.

A review of the pump calculations was required for requirement URD-23859-4-3 to determine that the right pipe and pump size had been specified.

The piping and layout drawings showed the quench tank T-402 as being in the same room as the reactor. Yet the requirement URD-23859-4-3 stated that the quench tank was to be in the isolation room. This turned out to be the only deviation so the meeting was adjourned and an investigation of the deviation was requested.

A review of meeting minutes was performed to determine why the location had been changed. The design team was notified of the findings and agreed that the true requirement was in the transfer time and not the location of the quench tank. The design team agreed to pass the verification of the equipment arrangement and piping drawings. An explanation was added to the DQ form.

Once the DQ on the system was completed and approved by XYZ Inc.'s Quality Assurance group, the design documents for the Cyclization Reactor were released to be issued for construction.

Design Firms and DQ

Most design firms have systems in place to review the design documents they produce. However, the needs of client companies can vary, and a design firm's procedures need to be adaptable to the expectations for DQ.

Procedures explaining the expectations of the design firms for DQ should be included with any RFPs. Should a client have particular needs that would be outside of the normal scope of deliverables, any additional costs would be reflected in a design firm's proposal.

Some of the systems and procedures that a client may request of a design firm for their DQ needs can help in controlling costs and "scope creep." Specific user requirement documents with traceability can be used for defining a design basis. Any feature or item in a design without a design history traceable back to the user's requirement could be flagged as a change for evaluation as a "must have" or a "nice to have."

Information usually flows in many parallel paths between a client and the design firm. Project Managers can more effectively manage a project and control scope by using an approved user requirement document as the official mechanism.

Multiple design firms or multiple disciplines may be involved in a project. Often, a client has a representative from a certain discipline work with a particular group within a design firm to create a specification for the project. These two parties may be in agreement with each other, since they both "speak the same language;" but qualification and validation involves many disciplines, and a design qualification needs to address all of them. Design firm disciplines need to all agree on the deliverables that will be used for DQ.

Summary

Pharmaceutical manufacturers may or may not have systems in place for performing DQ. The DQ procedures and expectations will vary from company to company. Design firms, vendors, and other support resources for pharmaceutical manufacturers need to understand the client's DQ needs and have systems and methods adaptable to those needs.

A clear agreement on the expectations for how facilities, systems, and equipment will be specified and which elements will require DQ is required by the entire design team. This should be addressed for each type of system. In particular, the client should be aware of the typical methodologies within each discipline of a design team.

DQ practices can improve the control of a project. The execution of a DQ should clearly identify:

- the document that established the "intended purpose of the proposed design"
- the documents that define the design
- the documents that were used to develop the design

The purpose of this article was to provide concepts, considerations, and examples that pharmaceutical industry professionals can use to help create or improve procedures for dealing with DQ. Remember, DQ, as stated by the ICH Q7A, is "the documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose."

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About the Author

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