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This article proposes an approach for qualification target selection and demonstrates how this can be applied to API manufacturing facilities.

Target Selection and Qualification – The Case of API Manufacturing Facilities

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Introduction

Industry associations and regulatory bodies indicate that qualification should be restricted to facilities and equipment that have an impact on product quality. However, the literature[1] does not provide guidelines for identifying facilities or equipment required to be qualified. For the establishment of facilities and equipment for API manufacture, statutory regulations require qualification of those facilities and equipment to be the manufacturer's (i.e., user's) responsibility. In Japan, there are a number of different interpretations of the regulatory requirements based on individual perceptions and understandings. Thus, the targets covered by the requirements and the qualification methods vary in accordance with the users' interpretations, yielding redundant qualification of facilities and equipment. Therefore, an adequate systematic approach for selecting qualification targets and determining qualification methods is necessary.

ICH published Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (ICH Q7) in November 2000.[1] Although it gives a definition of qualification, it does not explicitly define what must be qualified or how qualification should be performed.

ISPE published the *Baseline® Pharmaceutical Engineering Guide, Volume 5: Commissioning and Qualification (C&Q)*, a practical guide for qualification, in March 2001.[2] The Baseline Guide implies that qualification is required in addition to commissioning in accordance with Good Engineering Practice (GEP).

C&Q also asserts that a system impact assessment for facilities and equipment should be performed to classify the systems on the basis of their impacts on the quality of the product. The systems are classified into three groups: the direct impact systems, those that are critical to the quality of the product; the indirect impact systems, those that only indirectly affect it; and the no impact systems, those that have no impact on it. The components of the direct impact systems are then assessed for criticality and classified as critical components, which have a direct impact on the quality of the product, and noncritical components, which do not have such an impact. Qualification practices in addition to GEP should be applied exclusively to the critical components. Compliance with GEP only is sufficient for the noncritical components, the indirect impact systems, and the no impact systems.

The GMP Committee of the Japan Society of Pharmaceutical Machinery and Engineering (JSPME) has been studying a practical approach for selecting qualification targets and determining qualification methods since 2001. The committee published two case studies, one of a pan coating system in 2003,[3] and the other of blister filling/packaging systems and pillow packaging systems in 2007.[4] In addition, based on these studies, the committee also published a case study of an API manufacturing facility in 2008 as part of its joint research with the GMP Committee of the Japan Bulk Pharmaceutical Manufacturers Association (JBPMA).[5]

Extracting some portion from the case study of the API manufacturing facility, this article proposes a new approach for target selection and execution in qualification practices and also indicates how this approach can be applied to the reactor systems used for the production of intermediates and APIs. The concepts and definitions of qualification activities (DQ, IQ, OQ, and PQ) in this article are based on ICH Q7.

"In ordinary manufacturing processes, some of the important dynamic and static functions have a direct impact on the quality of the products, while the others have an indirect impact."

Fundamental Concepts of Target Selection and Execution

ICH Q7 states that before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. The authors propose the following fundamental concepts of qualification of the critical equipment and ancillary systems (hereinafter referred to as facilities and equipment) as to what should be qualified and how the actual qualification activities should be performed.

1. Facilities and equipment for API manufacture have various dynamic functions (work and action) which are performed by the static functions (structure, form, and material) of the facilities and equipment. Manufacturing API products using certain facilities and equipment entails utilizing such dynamic and static functions under prescribed conditions and within ranges of control to produce intended products. In ordinary manufacturing processes, some of the important dynamic and static functions have a direct impact on the quality of the products, while the others have an indirect impact.

   Here, product quality is linked to the ICH Q6A definition "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength, and purity" as described in ICH Q9.[6]

2. Quality risk assessment for those dynamic and static functions, based on the principle of ICH Q9[6], should be performed to classify the functions on the basis of their risks to the quality of the product. The functions are classified into two groups: the direct functions, those that have a risk of a direct impact on the quality of the product; and the indirect functions, those that have a risk of an indirect impact, or no risk of an impact on it.

   Qualification practices in addition to GEP should be applied exclusively to the direct functions. Compliance with GEP only is sufficient for the indirect functions.

3. The suitability and appropriateness of the facilities and equipment, regardless of their impacts on product quality, are verified, documented, and approved with GEP from the standpoint of quality risk at each stage of the engineering activities from design through commissioning.

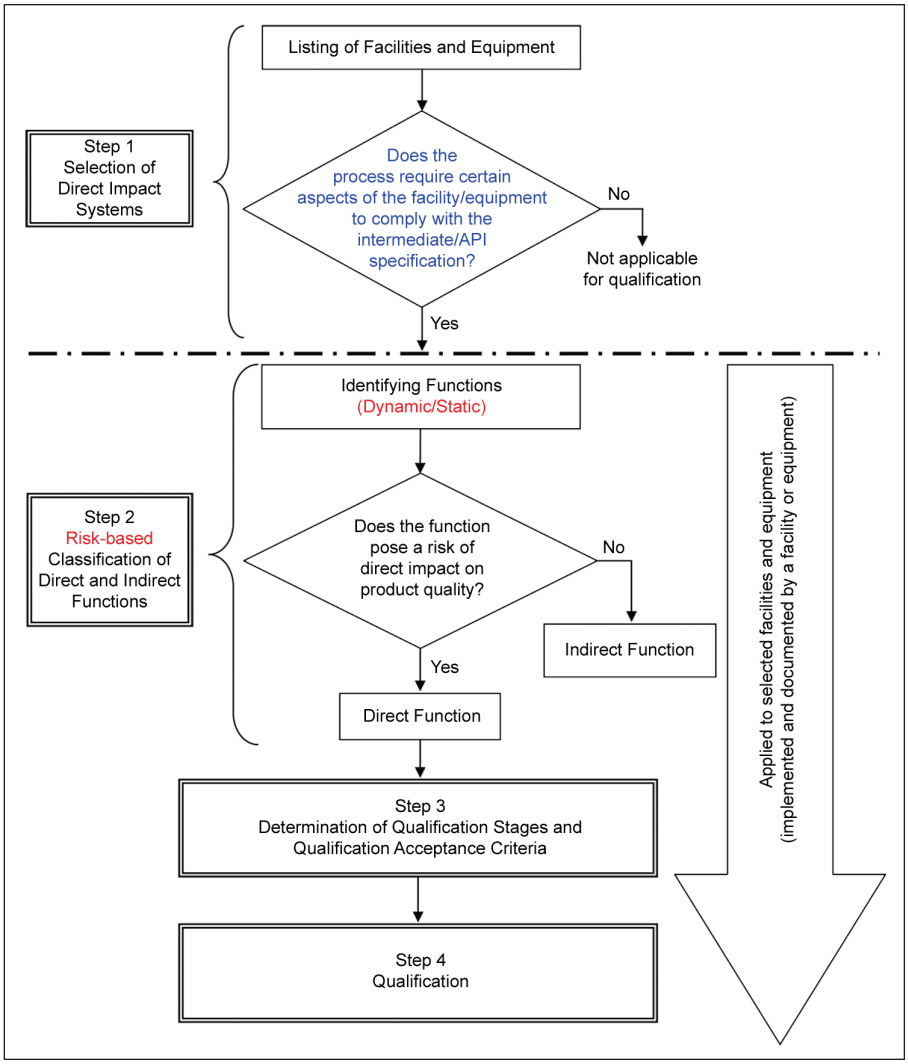

Figure 1. Work flowchart for qualification.

Facilities and Equipment Unit		Selection criterion satisfied?		Reason	Remarks
Name	Area	Yes (direct impact system)	No		
Reactor A System	Area shown in Figure 3	X		Reaction of key intermediates	

Table A. Selection of direct impact systems.

"Users do not necessarily need to duplicate the verification activities of the items that are already verified with the exception of the high level risk items mentioned later."

Therefore, it is sufficient for users in some qualification activities to confirm that these items are properly verified in the engineering activities. Users do not necessarily need to duplicate the verification activities of the items that are already verified with the exception of the high level risk items mentioned later. However, engineering change control should be applied to ensure that any changes made post verification are adequately addressed in respect to the impact of previously performed and completed verification activities. Qualification can be performed after all the engineering activities are completed, or it can be performed at an appropriate stage of the engineering activities: Design Qualification (DQ) at the design stage, Installation Qualification (IQ) and Operational Qualification (OQ) at the construction and commissioning stages.

	Class	Definition
Severity	5	Direct impact on product quality; reworking or destruction is required.
	4	Direct impact on product quality; reprocessing is required.
	3	No direct impact on product quality; recoverable in subsequent processes under standard manufacturing conditions even when deviations occur.
	2	No direct impact on product quality when manufacturing occurs under standard conditions.
	1	No impact on product quality

Table B. Severity classification (impact on product quality).

		Probability		
		Low	Medium	High
Severity	5	B	A	A
	4	B	B	A
	3	D	C	C
	2	E	D	C
	1	E	E	D

Table C. Level of risk.

Level of Risk	Scope of Qualification	Extent of Qualification
A	Applicable for qualification (Direct function)	Direct verification by user QA approval for documents
B		Supplier-prepared document review by user is permitted. QA approval for documents
C	Not applicable for qualification, verification under engineering practices (Indirect function)	Verification and documentation at engineering stage in accordance with risk level. Approval by head of related section.
D		
E		

Table D. Scope and extent of qualification.

Direct Functions	Qualification Stages			
	DQ	IQ	OQ	PQ
Static Direct Functions	→	→		
Dynamic Direct Functions	→	→	→	
Among Dynamic Direct Functions, Direct Functions Related to Process Control	→	→	→	→

Table E. Direct functions and qualification stages.

4. The direct functions are further classified as static direct functions (e.g., form, material, and surface finish) and dynamic direct functions (e.g. revolutions, temperature, and pressure). Dynamic direct functions can be further classified as either being subject to process control in the Standard Operating Procedure (SOP) or not.

5. If deemed critical, measurement and control devices and computerized control devices are targets of calibration and computerized system validation, and are not discussed in this article.

A New Method for Qualification Practice

Based on the concepts discussed in the previous section, the following explains the required activities and documentation in each stage of qualification using the flowchart in Figure 1.

Step 1: Selection of Direct Impact Systems

Among all the facilities and equipment, the facilities and equipment which have a direct impact on the quality (direct impact systems) are selected based on the selection criterion described below.

Selection criterion: Does the specified manufacturing process require

certain aspects of this facility/equipment to comply with the intermediate/API specification?

Examples of such manufacturing processes include the agitating processes of multiple ingredients, the phase conversion processes, the isolation processes (concentration or filtration), the temperature and pH sensitive processes, the processes that yield essential molecular components of the products, the intermediate processes in which principal chemical conversions take place, and the final purification processes. The selection is performed using a checklist as exemplified in Table A.

Step 2: Risk-Based Classification of Direct and Indirect Functions

For the direct impact systems selected in Step 1, dynamic and static functions having the potential to affect product quality are identified and classified through quality risk assessment in accordance with ICH Q9.[6,7]

Specifically, the risk-based classification of direct and indirect functions is performed in conformity with the contents of Tables B, C, D, and F. The quality risk assessment consists of risk identification, risk analysis, and risk evaluation as shown in Table F.

At the stage of risk identification, the dynamic functions and static functions are identified and challenged by the question, "What might go wrong?"

At the stage of risk analysis, the consequences are identified and their severity is classified in accordance with Table B. Also, the degree of probability that the unwanted event will occur is determined.

At the stage of risk evaluation, a level of risk is determined in accordance with the criteria shown in Table C. Then, the direct functions and indirect functions are classified using the following classification criterion.

Subsystem	Components	Quality Risk Assessment								Remarks
		Risk Identification		Risk Analysis			Risk Evaluation			
		Functions (Dynamic/Static)	What might go wrong?	What are the consequences?	Severity	Probability	Level of Risk	Direct Functions (Qualification Applied)	Indirect Functions (only GEP applied)	
Reactor System	Reactor Vessel A	Material (contacted process fluid)	Selected material not resistant to process fluid	Has impact on the purity of intermediate and product. Reworking or destruction is required when metal corroded material is mixed in process fluid.	5	L	B	X		
		Capacity	Capacity incorrectly defined	Has impact on productivity, but has no impact on quality of intermediate or of product.	1	L	E		X	
	Agitator	Material (contacted process fluid)	Selected material not resistant to process fluid	Has impact on purity of intermediate and product. Reworking or destruction is required when metal corroded material is mixed in process fluid.	5	L	B	X		
		Agitability	Insufficient study of scale-up	Has impact on impurity profile because of insufficient solid-liquid dispersion for proper reaction. Reprocessing is required when agitation is inadequate.	4	M	B	X		
		Revolution Speed		Individual functions have no direct impact on quality of intermediate and product as various combinations of these functions can achieve proper agitability.	2	M	D		X	
		Blade Shape			2	M	D		X	
		Blade Position			2	M	D		X	
		Motor Output			2	M	D		X	
Temperature Control System	Heat Source Unit, Controller	Reactive liquid temperature (condensation)	Incorrect temperature control range specified	Cause reaction time delay or abnormal reaction. Has impact on impurity profile when abnormal reaction occurs due to improper temperature control. Reworking or destruction is required when temperature is inadequate.	5	M	A	X		
Solvent Supply System	Piping	Material (contacted process fluid)	Selected material not resistant to process fluid	Has impact on purity of intermediate and product. Reworking or destruction is required when metal corroded material is mixed in process fluid.	5	L	B	X		
		Key: Probability L = Low, M = Medium, H = High								

Table F. Excerpt from example of risk-based classification of direct and indirect functions (Reactor A system).

"Qualification activities (i.e., DQ, IQ, OQ, and PQ) determined in Step 3 are performed and documented in this step. The qualification activities are implemented and reported in accordance with the pre-approved protocol."

Classification criterion: dynamic and static functions that can pose a risk of direct impact on the quality of the product (Severity Class 4 and 5 shown in Table B) are direct functions, while others (Severity Class 1, 2, and 3 shown in Table B) are indirect functions.

The scope and extent of qualification is determined by the level of risk as outlined in Table D.

Step 3: Determination of Qualification Stages and Qualification Acceptance Criteria

In this step, required qualification stages are determined for each direct function obtained in Step 2 in accordance with the criteria shown in Table E.

The acceptance criteria for each direct function in determined qualification stages are also established at this step.

Table G is an excerpt from an example of the determination of qualification stages and qualification acceptance criteria. This table is useful for capturing the entire picture of qualification to facilitate its smooth execution as the table comprehensively shows direct functions (items and contents) as well as required qualification activities and acceptance criteria.

Step 4: Qualification

Qualification activities (i.e., DQ, IQ, OQ, and PQ) determined in Step 3 are performed and documented in this step. The qualification activities are implemented and reported in accordance with the pre-approved protocol. Examples of data sheet formats (part of reports) are shown in Tables H to K.

Outline of API Manufacturing Facilities

This section introduces the outline of API manufacturing facilities and equipment to be studied in applying the new method proposed in Section 2.

The Manufacturing Process of API Intermediate

Compounds A and B, potassium carbonate, and dimethylformamide are agitated at 25°C for 24 hours. Then sodium borohydride, suspended in dimethylformamide, is dropped into the admixture in the presence of N2 gas, keeping the temperature of the reaction solution below 35°C. The admixture is agitated at 25°C for another 24 hours to obtain an intermediate (intermediate C). Figure 2 is a block flow diagram of the manufacturing process.

Components and Functions of the Reactor A System

The major equipment and instruments

Subsystem	Components	Direct Functions		Qualification Stage and Qualification Acceptance Criteria					Remarks
		Level of Risk	Items	Contents	DQ	IQ	OQ	PQ	
Reactor System	Reactor Vessel A	B	Material (contacted process fluid)	Resistance to corrosion in acid and alkali	Glass lining	Glass lining	-	-	
				Chemical resistant gaskets	Fluororesin gasket	Fluororesin gasket	-	-	
	Agitator	B	Material (contacted process fluid)	Resistance to corrosion in acid and alkali	Glass lining	Glass lining	-	-	
				Chemical resistant gaskets	Fluororesin gasket	Fluororesin gasket	-	-	
		B	Agitatability	Solid-liquid dispersion (reagent in DMF)	Designed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm)	Installed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm)	Agitator operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm)	Potassium carbonate to be dispersed under agitation after charging 6 0L DMF and 11.8 kg potassium carbonate into the Reactor Vessel A	
Below Omitted									

Table G. Excerpt from example of determination of qualification stages and qualification acceptance criteria (Reactor A system).

Subsystem	Components	Direct Functions			DQ Acceptance Criteria	Verified Doc. Name/ No. (Note)	Result	Date	Sign	Remarks
		Level of Risk	Items	Contents						
Reactor System	Reactor Vessel A	B	Material (contacted process fluid)	Resistance to corrosion in acid and alkali	Glass lining		OK/NG			
				Chemical resistant gaskets	Fluororesin gasket		OK/NG			
	Agitator	B	Material (contacted process fluid)	Resistance to corrosion in acid and alkali	Glass lining		OK/NG			
				Chemical resistant gaskets	Fluororesin gasket		OK/NG			
		B	Agitatability	Solid-liquid dispersion (reagent in DMF)	Designed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm)		OK/NG			
Below Omitted										
Note: Refer to attachment for verified documents.										

Table H. Excerpt from example of a DQ report (Reactor A system).

of the Reactor A system are illustrated in Figure 3. This system is composed of the following six subsystems:

1. Reactor system: performs the chemical reaction of compounds; composed of a Reactor Vessel A, an agitator, and an agitator controller.

2. Temperature control system: controls the temperature of the Reactor Vessel A; composed of a thermometer, a heat source unit, a pump, piping, and a controller.

3. Solvent supply system: supplies solvent to the Reactor Vessel A and the Dropping Vessel A; composed of piping.

4. Dropping system: drops sodium borohydride suspended in dimethylformamide into the Reactor Vessel A; composed of a Dropping Vessel A, a pump and piping.

5. N2 gas supply system: supplies N2 gas to the Reactor Vessel A and the Dropping Vessel A; composed of a flow meter, piping, and a filter, etc.

6. DCS: controls the manufacturing process; subject to computerized system validation.

Subsystem	Components	Direct Functions			IQ Acceptance Criteria	Test Method	Verified Doc. Name/No. (Note 2)	Result	Date	Sign	Remarks
		Level of Risk	Items	Contents							
Reactor System	Reactor Vessel A	B	Material (contacted process fluid)	Resistance to corrosion in acid and alkali	Glass lining	Visual		OK/NG			
				Chemical resistant gaskets	Fluororesin gasket	Visual		OK/NG			
	Agitator	B	Material (contacted process fluid)	Resistance to corrosion in acid and alkali	Glass lining	Visual		OK/NG			
				Chemical resistant gaskets	Fluororesin gasket	Visual		OK/NG			
		A	Agitatability	Solid-liquid dispersion (reagent in DMF)	Installed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm)	Verify with designed documents checked/ verified in DQ (Note 1)		OK/NG			
Below Omitted											

Note 1: If drawings and specifications are revised after DQ completion, re-DQ must be done for the drawings and specifications prior to IQ start. Change control is required in the case of any change.
Note 2: Refer to attachment for verified documents.

Table I. Excerpt from example of an IQ report (Reactor A system).

Subsystem	Components	Direct Functions			OQ Acceptance Criteria	Test Method	Verified Doc. Name/No. (Note 2)	Result	Date	Sign	Remarks
		Level of Risk	Items	Contents							
Reactor System	Agitator	B	Agitatability	Solid-liquid dispersion (reagent in DMF)	Agitator operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm)	Water operation		OK/NG			
Temperature Control System	Heat Source Unit, Controller	A	Reactive liquid temperature (condensation)	Mixture of Compounds A and B, potassium carbonate and DMF to be kept at 25 ±5°C for 24 hours	Temperature control system operating conditions: (i) temperature (XX ~ YY °C) (ii) liquid level (min. xx ~ max. yy mm)	Water operation (Note 1)		OK/NG			
		A	Reactive liquid temperature (reduction)	Reactive liquid to be kept at 25 ±5°C for 24 hours after charging DMF suspension liquid of sodium borohydride							
Below Omitted											

Note 1: The temperature range that cannot be verified by water operation is verified in PQ.
Note 2: Refer to attachment for verified documents.

Table J. Excerpt from example of an OQ report (Reactor A system).

A Case Study of the New Qualification Method

This section describes a case study of the new qualification method applied to the Reactor A system. The description follows the steps shown in Figure 1 except for Step 1 where direct impact systems are selected, referring to Table A.

Step 2: Risk-Based Classification of Direct and Indirect Functions

Table F shows how the components in each subsystem shown in Figure 2 and the direct and indirect functions are classified through the quality risk assessment described in Section 2-2.

Step 3: Determination of Qualification Stages and Qualification Acceptance Criteria

Table G is a list of qualification stages and qualification acceptance criteria for the direct functions selected in Step 2.

Step 4: Qualification

Since the requirements of good documentation practice (version control, etc.) for qualification protocols and reports are widely known throughout the pharmaceutical industry, this article focuses on the content and structure of the documents. The following text describes the content and should be read in parallel with Tables A, B, C, and D, where the Tables provide the structure.

DQ

The DQ protocol describes 1) subsystems, 2) components, 3) direct functions (level of risk, items, and contents), and 4) the DQ acceptance criteria. The DQ report includes the description of the documents checked or verified, the results, etc., as well as 1) to 4) of the DQ protocol. Table H is an excerpt from an example of a DQ report. (It also includes the requirements of the DQ protocol.)

IQ

The IQ protocol describes 1) to 3) of the DQ protocol, the IQ acceptance criteria, and the test method. The IQ

report includes the description of the documents checked or verified, the results, etc., in addition to all the items in the IQ protocol. Table I is an excerpt from an example of an IQ report. (It also includes the requirements of the IQ protocol.)

OQ

Targets in the OQ are only the dynamic direct functions. The OQ protocol describes the relevant items among 1) to 3) of the DQ protocol. It also should describe the OQ acceptance criteria and the test methods. The OQ report should include the description of the documents checked or verified, the results, etc., in addition to all the items in the OQ protocol. Table J is an excerpt from an example of an OQ report. (It also includes the requirements of the OQ protocol.)

PQ

Targets in the PQ, which is always performed at the user's site, are restricted to the dynamic direct functions that are subject to process control. The PQ protocol should describe the relevant items among 1) to 3) of the DQ protocol. It also should describe the PQ acceptance criteria and the test method. The PQ report should include the description of the documents checked or verified, the results, etc., in addition to all the items in the PQ protocol. Table K is an excerpt from an example of a PQ report. (It also includes the requirements of the PQ protocol.)

Conclusion

The authors propose a new approach for the target selection and execution of qualification practices by quality risk assessment based on the principles of ICH Q9.[6] This new approach is explained for the Reactor A system used in the production of an intermediate, for example. An outline is provided as follows.

Facilities and equipment for API manufacture have various dynamic functions (work and action) which are performed by the static functions (structure, form, and material) of the facilities and equipment. It is necessary to execute such dynamic and static functions under prescribed conditions and within ranges of control to produce the intended products. However, only some of the dynamic and static functions in the critical processes have a direct impact on the quality of the product, while other dynamic and static functions have indirect impact, and others exist in non critical processes.

Quality risk assessment for those dynamic and static functions, based on the principle of ICH Q9,[6] should be performed to classify the functions on the basis of their risks to the quality of the product. Functions are classified into two groups: direct functions, those that have a risk of a direct impact on the quality of the product; and indirect functions, those that have a risk of an indirect impact on or no risk of impact on it.

Qualification practices in addition to GEP should be applied exclusively to the direct functions. Compliance with GEP only is sufficient for the indirect functions.

Qualification execution consists of the following steps:

Subsystem	Components	Direct Functions			PQ Acceptance Criteria	Test Method	Verified Doc. Name/No. (Note)	Result	Date	Sign	Remarks
		Level of Risk	Items	Contents							
Reactor System	Agitator	B	Agitatability	Solid-liquid dispersion (reagent in DMF)	Potassium carbonate to be dispersed under agitation after charging 60 L DMF and 11.8 kg potassium carbonate into the Reactor Vessel A	Visual		OK/NG			
Temperature Control System	Heat Source Unit, Controller	A	Reactive liquid temperature (condensation)	Mixture of Compounds A and B, potassium carbonate and DMF to be kept at 25±5°C for 24 hours	Temperature to be controlled at 25±5°C for hours after charging the specified amounts of compounds A and B, potassium carbonate and DFM according to the procedure	Record by temperature recorder		OK/NG			
		A	Reactive liquid temperature (reduction)	Reactive liquid to be kept at 25 ±5°C for 24 hours after charging DMF suspension liquid of sodium borohydride	Maximum temperature to be below 35°C during dropping and kept at 25±5°C for 24 hours after dropping under the conditions of specified amount of charge volume of sodium borohydride/DMF	Use thermometer and stopwatch		OK/NG			
Below Omitted											
Note: Refer to attachment for verified documents.											

Table K. Excerpt from example of a PQ report (Reactor A system).

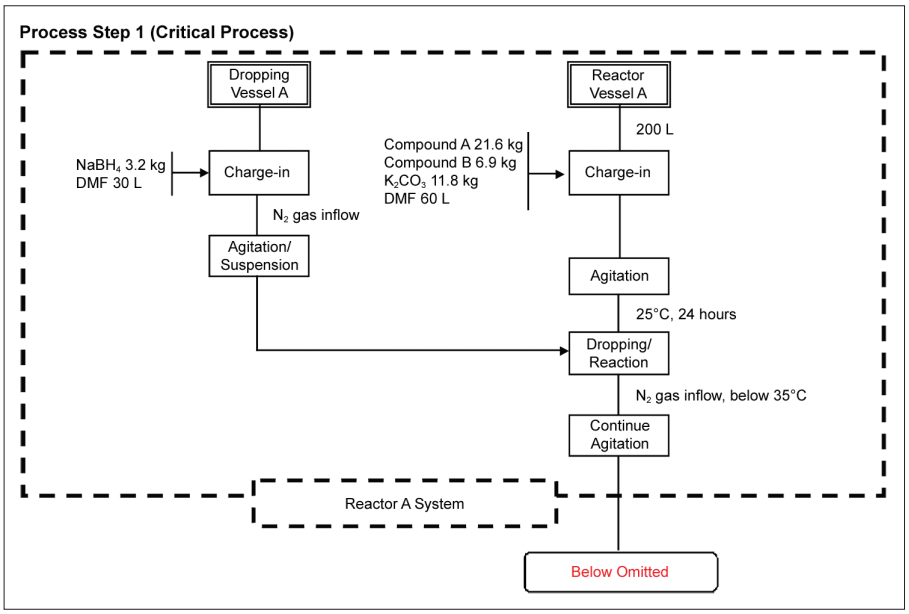

Figure 2. Manufacturing block flow diagram for intermediate products.

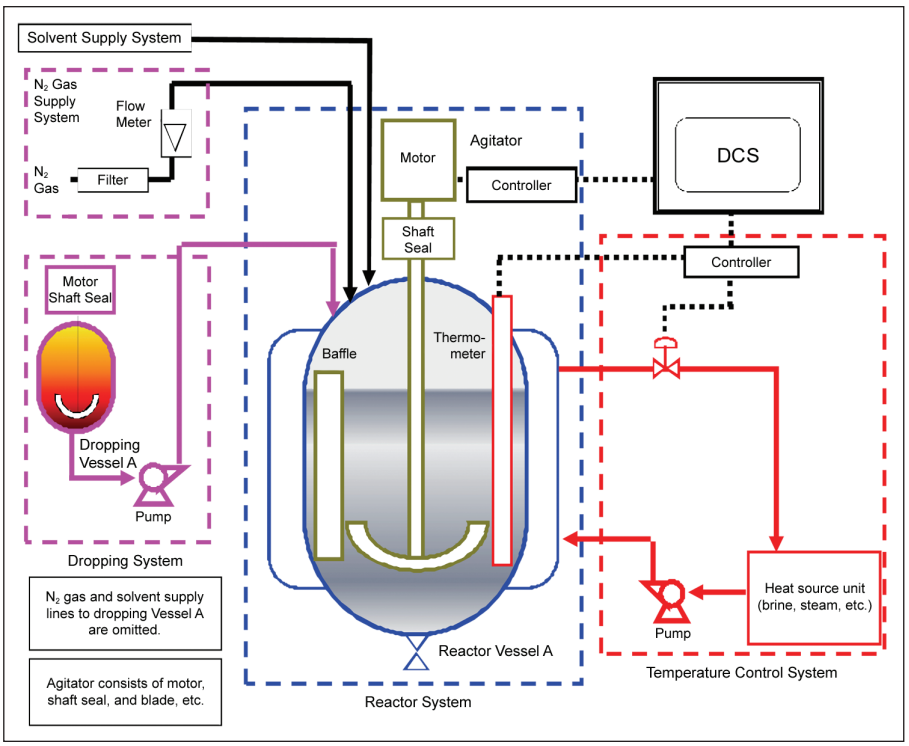

Figure 3. Equipment and instruments of Reactor A system.

1. Select direct impact systems used in critical manufacturing processes.

2. Identify functions (Dynamic/Static) of the direct impact systems and then classify them as either direct or indirect functions in accordance with the level of quality risk determined by risk assessment.

3. Determine qualification stages and qualification acceptance criteria. Static direct functions are to be the targets of DQ and IQ. Dynamic direct functions not subject to process control are to be the targets of DQ through OQ. Dynamic direct functions subject to process control are to be the targets of DQ through PQ.

4. Prepare protocol, implement and prepare a report at each stage of qualification.

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About the Authors

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JSPME is a non-profit volunteer society founded in 1991 in order to advance pharmaceutical technology through the exchange of knowledge and experience in a wide range of industries related to pharmaceutical production.

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GMP Committee, Japan Bulk Pharmaceutical Manufacturers Association (JBPMA)

JBPMA is a nationwide association comprised of member companies who engage in the manufacture and sales of bulk and intermediate pharmaceuticals. The association was founded in 1975 aiming at the establishment of the Active Pharmaceutical Ingredient (API) GMP and a quality assurance system, etc.

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