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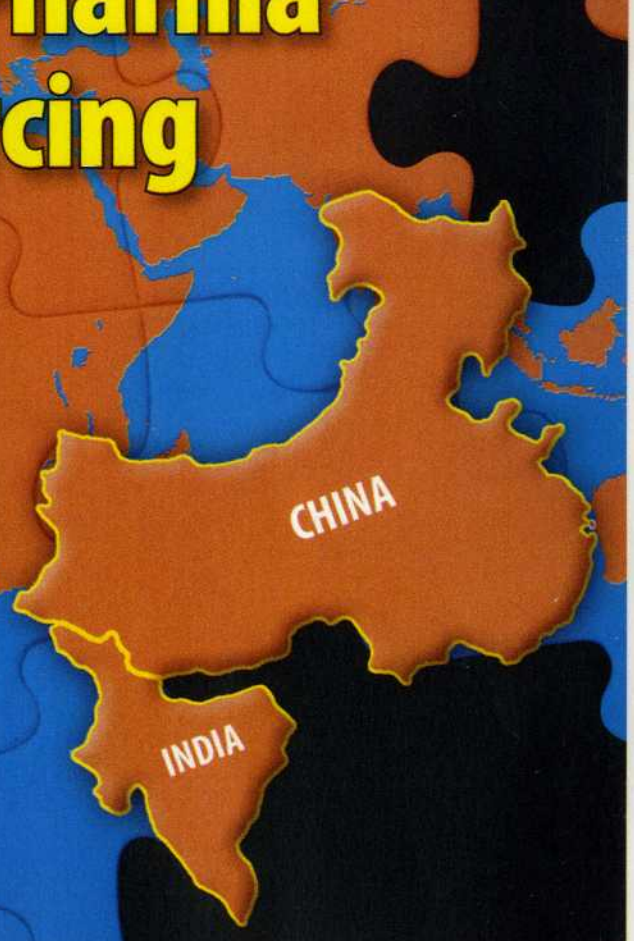

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Postapproval Management Plans

Qualifying Blister-Filling and Packaging Systems

Integrating Large-Scale Chromatography with Nanofiltration

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VALIDATION

Target Selection and Qualification

The Case of Blister-Filling and Packaging Systems

Toyohiko Takeda and Hiroshi Hirasawa

Industry associations and regulatory bodies indicate that qualification should be restricted to systems and equipment that have a direct effect on product quality. The literature does not provide guidelines for identifying critical equipment, however. The authors propose an approach for qualification-target selection and show how it can be applied to blister-filling and packaging systems.

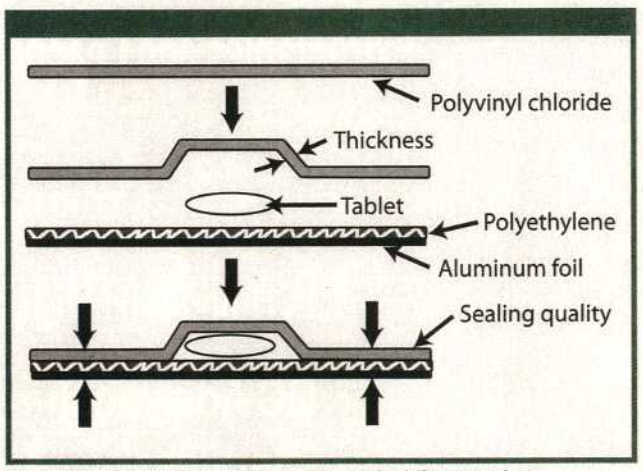

Figure 1: The manufacturing process of a blister pocket.

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Regulations that control the construction of facilities and equipment for medical-product manufacturing require qualification of the facilities and equipment. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use defines the common principles of the qualification of ingredients, formulations, and packaging (1). However, it does not clearly define the methods for determining what must be qualified or for performing qualification.

In its guideline on commissioning and qualification (C&Q), the International Society for Pharmaceutical Engineering (ISPE) states that qualification practices are required after commissioning to provide supplementary assurance that good engineering practices (GEP) have been followed (2).

ISPE says that a system-impact assessment should be performed first to identify the systems that have a direct effect on the quality of the product. The components or devices of the direct-impact systems should then be classified as critical components, which have a direct effect on the quality of the product, and noncritical components, which do not. Qualification practices should only be applied to the critical components. Adherence to GEP is sufficient for indirect-impact systems and noncritical components.

ISPE's C&Q document, however, mentions an exceptionally broad range of criteria for identifying critical components. The document does not describe in detail how to determine which critical components must be qualified or how to qualify them. For these reasons, various methods for selecting targets and performing qualification have emerged. In many cases, components are qualified even when they are not required to be.

The Good Manufacturing Practice (GMP) Committee of the Japan Society of Pharmaceutical Machinery and Engineering has studied qualification practices for systems used in solid-dosage-form facilities, including pan-coating systems, blister-filling and packaging systems, and pillow-packaging systems (3, 4). On the basis of these studies, this article proposes a new approach to target selection and qualification and shows how the approach can be applied to blister-filling and packaging systems.

ALL FIGURES ARE COURTESY OF THE AUTHORS AND THE JAPAN SOCIETY OF PHARMACEUTICAL MACHINERY AND ENGINEERING.

Selecting the targets of qualification

ICH's Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* states that appropriate qualification of critical equipment and ancillary systems should be completed before starting process-validation activities. This section will explain which components of the critical equipment and ancillary systems should be selected as targets of qualification.

Medical-product manufacturing systems have various functions that are performed by the systems' mechanism, shape, and material. Using a certain system to manufacture medical products entails executing the system's functions under prescribed, controlled conditions. In ordinary manufacturing processes, some system functions have a direct effect on the quality of the products and others have an indirect effect.

The authors believe that qualification of critical equipment and ancillary systems should be interpreted as qualification of system functions that have a direct effect on product quality. The article will apply this principle to qualification-target selection, using blister-filling and packaging systems as an example. First, the quality of the products should be explained. The quality of blister products can be defined in terms of protecting their contents (e.g., tablets) and display or identification. This article focuses on the former function. The authors define the thickness of the blister pocket web as a critical factor that directly affects product protection.

Blister-filling and packaging systems are direct-impact systems because they directly affect the quality of blister-package products. An examination of the systems' operating principles shows that the forming function and the speed-control function directly affect the thickness of the blister pocket web. Furthermore, a close examination of the system devices that affect the forming function shows that the heating device and the forming device directly affect the thickness of the blister pocket web.

Parts of the heating and the forming devices directly affect web thickness, and the functions of these critical parts should be identified. For example, manufacturers should determine the function of the heating device's heating plate and that of the forming device's forming die. In this case, the required function is that of assigning the appropriate quantity of heat or shape and size to the plastic film. Because the quantity of heat is usually difficult to measure or control, however, the temperature of the heating plate should be measured and controlled instead.

The temperature of the heating plate and the shape and size of the forming die are called *direct factors.* Qualification should be restricted to these direct factors.

Other devices (e.g., the plastic-film-feeding device) and their corresponding functions (e.g., the plastic-film-feeding function) should follow GEP but do not require qualification.

In principle, qualifications are carried out after GEP are applied. But the stages from design qualification (DQ) to operational qualification (OQ) can be carried out in parallel with GEP according to a prior plan to avoid duplicate application or backtracking.

Table I: Major functions and devices of blister-filling and packaging systems.

No.	Function	Major device	
1	Film feeding	1 2	Web film–feeding device Lid film–feeding device
2	Forming	3 4 5	Heating device Forming device Web film–feeding device
3	Filling	6	Filling device
4	Inspecting	7	Inspection device
5	Sealing	8	Sealing device
6	Slitting	9 10	Slitting device Film-feeding device
7	Embossing	11 10	Embossing device Film-feeding device
8	Punching	12 10	Punching device Film-feeding device
9	Handling	13	Scrap-cutting device
10	Accumulation	14	Accumulation device
11	Speed control	15	Speed-control device

Direct factors are classified as *dynamic factors* (e.g., the plate temperature of the heating device) and *static factors* (e.g., the shape and size of the forming die). Dynamic factors are further classified as either being subject to process control or not. The overall classification of direct factors is as follows:

- Class 1: Dynamic factors that affect quality
- Class 1-A: Dynamic factors subject to process control
- Class 1-B: Dynamic factors not subject to process control
- Class 2: Static factors that affect quality.

Class 1-A factors can be changed when the system is in operation. They should be observed, recorded, and adjusted so that they stay within the predefined control range.

Class 1-B factors cannot be changed when the system is in operation. They should be set or adjusted in advance of operation.

Class 2 factors (e.g., material, configuration, and surface finish) are fixed when the system is constructed and, in principle, do not change afterward.

Devices used to measure and control the dynamic factors and computerized control devices must be calibrated and validated, respectively. Calibration and computerized-system validation should occur before the start of OQ, which is the third stage of qualification.

The following precautions are important for constructing medical manufacturing systems and should all adhere to GMP:

- Protection against foreign substances
- Ensuring the correct product is packaged
- Protection against cross contamination.

These precautions relate chiefly to the working environment, working control, and maintenance checks. They can be taken independently of the systems. Therefore, the func-

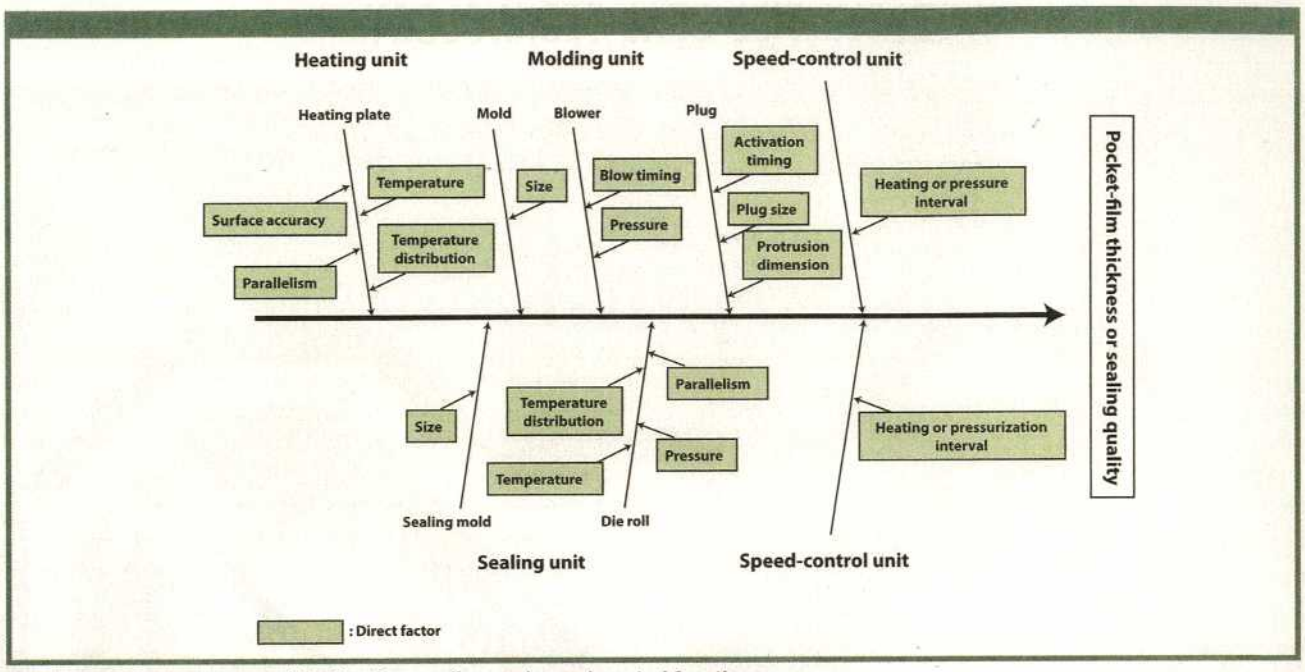

Figure 2: The direct factors of the forming, sealing, and speed-control functions.

tions and devices related to the items above are not subject to qualification and should simply follow GEP.

Direct factors of blister-filling and packaging systems

Quality of blister products. Blister packages should protect their contents (e.g., tablets) to control their stability, dissolution, and disintegration. This article takes the protective function of blister packages as one element of the required quality for blister products.

The important elements of product protection are appropriate web thickness, which prevents vapor or oxygen-gas ingress, and proper sealing, which maintains airtight pockets (see Figure 1).

Criteria for screening the functions. The following criteria should be used to identify the devices and parts of blister-filling and packaging systems that are direct-impact factors:

- Whether the given function affects web film thickness
- Whether the given function affects the seal quality.

Functions and devices of blister-filling and packaging systems. Blister-filling and packaging systems consist of 11 major functions and 15 major devices as listed in Table I. The forming function, the sealing function, and the speed-control function directly affect web film thickness and seal quality. The speed-control function controls the duration of the heating and pressing processes.

A fishbone diagram of the direct factors of blister-filling and packaging systems. Figure 2 is a fishbone diagram of the direct factors of the forming, sealing, and speed-control functions. The important devices for fulfilling the forming, sealing, and speed-control functions are the heating device, the forming device, the sealing device, and the speed-control device. The following parts of those devices affect the web thickness or the sealing quality: the heating plate of the heating device; the forming die, the forming blower, and the plug of the forming device; and the sealing die and the die roll of the sealing device (see Table II).

For example, the required function of the heating plate is to uniformly transmit a prescribed quantity of heat to the plastic film.

According to the above principles, the temperature, temperature distribution, surface accuracy, and parallelism between the upper and the lower heating plates are direct factors. The same principles apply to the other three devices (see Figure 2).

The other devices in blister-filling and packaging systems do not include direct factors. Table II shows a classification of the direct factors in Figure 2 based on the discussion above.

Direct factors of blister-filling and packaging systems and qualification

Required qualification stages of direct factors. Table III shows the required qualification stages for each class of direct factors in Table II.

Stages from DQ to performance qualification (PQ) are required for dynamic factors in Class 1-A, which are subject to the process control prescribed in the product master formula. Stages from DQ to OQ are required for dynamic factors in Class 1-B, which are not subject to process control. However, PQ also may be required for Class 1-B factors when the run speed is the only factor to be changed. Usually run speed is constant, but when this speed must be changed for some reason, the modified speed could be controlled in the process, as represented by the dotted arrow in Table III. Static factors require DQ and installation qualification (IQ).

Table II: Classification of direct factors of blister-filling and packing systems.

Important factor of product quality	Major device relevant to important factor	Part relevant to important factor	Direct factor	Class
Web thickness	Heating device	Heating plate	Plate temperature	1-A
			Temperature distribution	2
			Parallelism	2
			Surface accuracy	2
	Forming device	Forming die	Forming die size	2
		Forming blower	Forming blow timing	1-B
			Forming blow pressure	1-A
		Plug	Plug size	2
			Protrusion dimension	2
			Activation timing	1-B
Sealing quality	Sealing device	Sealing die	Sealing die size	2
		Die roll	Die roll temperature	1-A
			Die roll temperature distribution	2
			Die roll pressure	1-A
			Parallelism between sealing die and die roll	2
Web thickness Sealing quality	Speed control device		Heating/pressing time	1-B

Examples of qualification stages from DQ to PQ. This subsection presents examples of items that must be described in an implementation plan and an implementation report of qualification from DQ to PQ. Two of the direct factors of the heating plate (i.e., the heating plate temperature and parallelism) are used as examples.

An example of DQ. The devices and parts that affect the heating-plate temperature and parallelism listed in the requirements specification must be properly documented in the manufacturing specification. The location of the confirmed items in the requirement specification and the manufacturing specification must be recorded in the report.

At minimum, the following items must be described in the DQ implementation plan: the important product-quality factor (i.e., web thickness of 50 μm), the direct factors (i.e., heating-plate temperature and parallelism), and the assessment procedure.

At minimum, the following items must be described in the DQ report: the important product-quality factor, the document to be verified or confirmed (i.e., the document number of the requirements specification, the page numbers of the relevant items, the document number of the manufacturing specification, and the page numbers of the relevant items), the result, the date, and the inspector.

An example of IQ. The devices and parts that affect the heating-plate temperature must be installed according to the manufacturing specification, and the heating-plate parallelism must conform to the criteria in the IQ implementation plan. The results must be recorded in the IQ report.

At minimum, the following items must be described in the IQ implementation plan: the important product-quality factor, the direct factors, the criteria (i.e., installation of the heating device according to the manufacturing specification and within acceptable margin of parallelism), and the assessment procedure.

At minimum, the following items must be described in the IQ report: the direct factors, the criteria, the results, the judgment, the date, and the inspector.

An example of OQ. The heating-plate temperature must conform to the criteria in the OQ implementation plan. The results must be recorded in the OQ report.

At the OQ stage, the temperature of a versatile heating plate that can be used for different products is usually examined. However, if the plastic film used for these products is the same and the required web thickness is also the same, then OQ and PQ can be combined.

At minimum, the following items must be described in the OQ implementation plan: the important product-quality factor, the direct factors, the criteria (i.e., preset temperature and permissible fluctuation), and the assessment procedure.

At minimum, the following items must be described in the OQ report: the direct factors, the criteria, the results, the judgment, the date, and the inspector.

An example of PQ. The heating-plate temperature specified in the product master formula must conform to the criteria in the PQ implementation plan. The results must be recorded in the PQ report.

At minimum, the following items must be described in the PQ implementation plan: the important product-quality factor, the direct factors, the criteria (i.e., preset temperature and permissible fluctuation), and the assessment procedure.

At minimum, the following items must be described in the PQ report: the direct factors, the criteria, the results, the judgment, the date, and the inspector.

Conclusion

The authors propose a new approach to target selection and implementation of qualification that can be summarized by the following points:

- Product quality and the factors that influence it (i.e., the important factors) must be defined.
- The critical functions of the devices and parts that directly affect the important factors must be specified.
- The factors (e.g., pressure and heat) that the critical functions assign to the objects of the manufacturing process must be defined.

Table III: Qualification stages of direct factors of blister-filling and packing systems.

Class		Direct factor	Stage of qualification			
			DQ	IQ	OQ	PQ
Dynamic factor	1-A	Heating device: Plate temperature				
		Forming device: Blow pressure				
		Sealing device: Die roll temperature				
		Sealing device: Die roll pressure				
	1-B	Forming device: Blow timing				
		Forming device: Plug activation timing				
		Speed control device: Heating/Pressing time				
Static factor	2	Heating device: Plate temperature distribution				
		Heating device: Plate parallelism				
		Heating device: Plate surface accuracy				
		Forming device: Die size				
		Forming device: Plug size				
		Forming device: Protrusion dimension				
		Sealing device: Sealing die size				
		Sealing device: Die roll temperature distribution				
		Sealing device: Parallelism between forming die and die roll				

- The above factors are direct factors and should be taken as the sole targets of qualification.
- Direct factors should be classified as either dynamic or static factors. Dynamic factors should be further classified as either subject to the process control or not.
- Required stages of qualification should be determined according to the above classifications.
- Indirect factors must follow GEP, but do not require qualification.

This proposal should aid the practical implementation of qualification. The authors welcome readers' comments.

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