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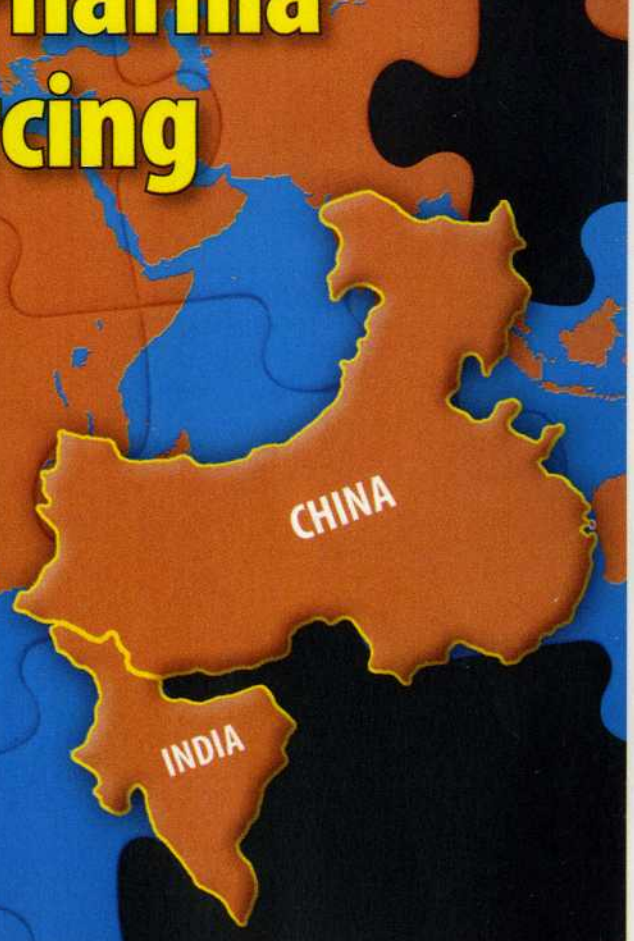

PEER-REVIEWED

Postapproval Management Plans

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Jim Miller's Outsourcing Outlook: *Survival of the Fittest Companies*

PEER-REVIEWED

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.

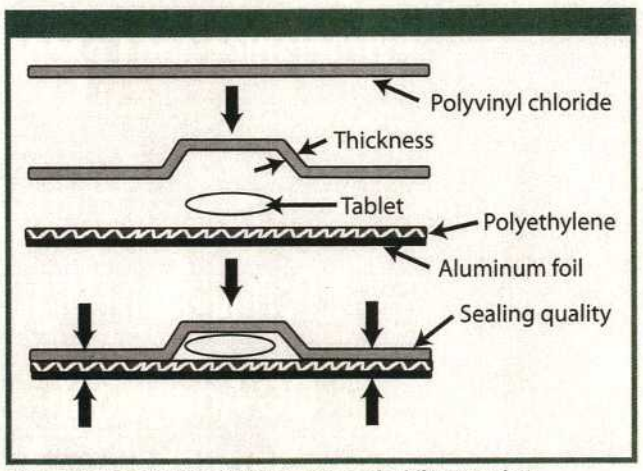

Figure 1: The manufacturing process of a blister pocket.

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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-