Good Manufacturing Practices

(PHAR 533)

Fifth Grade – Spring Semester

Faculty of Pharmacy
Pharmacy Department
Tishk International University

Lecture 5

Production and Process Controls

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Outlines

- Process Validation

1. Process Design
2. Process Performance Qualification
3. Continued Process Verification

- Control of Microbiological Contamination

Learning Outcomes

At the end of this chapter, you will be able to:

1. Explain the concept and lifecycle of process validation, including process design, process performance qualification, and continued process verification.
2. Apply GMP principles to process design and qualification.
3. Describe GMP strategies for controlling microbiological contamination and distinguish between terminal sterilization and aseptic processing in pharmaceutical manufacturing.

Process Validation

The collection and evaluation of data, from process design to commercial production, establishes **scientific evidence** that a process is capable of consistently delivering quality products.

The **activities** involved in **process validation** occur over the entire life cycle of a product and can be divided into three stages:

1. Process Design
2. Process Performance Qualification
3. Continued Process Verification

Process Validation

1. Process Design

The **commercial manufacturing processes** are defined during Stage I, based on knowledge gained through development of the process, site transfer, and scale-up activities.

Risk assessment will be conducted during the process design stage to select critical process steps and parameters.

Documentation, including process flow diagrams with information regarding critical set points, inputs, and the expected outputs, will be established.

Process Validation

1. Process Design

Factors to be considered in the process design stage include:

- The functionality and limitations of commercial manufacturing equipment.
- The variability that may be caused by different production lots, production operators, environmental conditions, and measurement systems in the production setting.

Process Validation

2. Process Performance Qualification

During this stage, the process design is evaluated to determine if it is capable of reproducible results during commercial manufacturing.

This stage is equivalent to **process validation**, which must be done according to a pre-approved protocol, and sampling is to be performed at a higher level than the normal quality sampling of a batch.

Process Validation

2. Process Performance Qualification

The **number of batches required for validation** must be scientifically justified, using statistical measures to achieve adequate assurance.

Factors that affect the number of required batches include:

- The process complexity
- The level of process variability.

The completion of Stage II is the equivalent of reaching a "validated state" for the process.

Process Validation

3. Continued Process Verification

This stage assures that the manufacturing processes are in a continuous state of control during routine commercial production. A program is established to collect and analyze product and critical process data on a regular basis.

An annual review of validation status is also an important part of this process.

Review of:

- Deviations
- Product failures
- Complaints
- Other product performance and quality indicators

Process Validation

3. Continued Process Verification

If **significant deficiencies** are identified during review of the current validation package, the need for complete revalidation must be assessed.

A process may require **revalidation** due to an increase in variability or a change in the process. When a process change is proposed, the extent of revalidation required must be based on an assessment of the impact of the change on the critical quality elements of the process.

Process Validation

3. Continued Process Verification

At a minimum, the following must be considered in revalidation:

- Changes in the master manufacturing formula, procedure, or batch size
- Changes in validated ranges of process parameters
- Raw materials, grade, reference standards, or test methods
- Changes to the container closure system
- Changes to equipment, instrumentation, or computerized systems or their maintenance
- Changes to facilities

Control of Microbiological Contamination

For most products **other than** injections and eye preparations, there is no need for sterility. For these products, the presence of microorganisms could still constitute a problem since certain microorganisms are associated with human illness and must be absent.

The presence of certain microorganisms in **nonsterile preparations** may have the potential to reduce or even inactivate the therapeutic activity of the product (loss of active ingredient or breakdown in physical characteristics, such as emulsions) and has a potential to adversely affect the health of the patient.

In such cases, it may be necessary to have a specification for total viable microorganisms.

Control of Microbiological Contamination

The procedures and conditions required to assure adequate microbial control:

1. Microbial monitoring of potentially susceptible raw materials (materials of natural origin), those likely to support microbial growth, and materials to be used in product formulations, such as injections.
2. Equipment sanitation procedures that have been proven.
3. Processing conditions that minimize the potential for microbial growth.
4. Environmental control, including covers over equipment; laminar flow at susceptible points, wearing of protective clothing such as gloves and masks, and clearing filling lines at breaks.
5. Formulations to include preservatives.

Control of Microbiological Contamination

Sterile products are manufactured using either terminal sterilization or aseptic processing.

The level of sterility assurance is significantly higher with **terminal sterilization**; autoclaving at 121°C can result in a 10^{-6} microbial survivor probability, whereas aseptic processing tends to result in the order of 10^{-3}.

Because of these significant differences in assurance levels, **terminal sterilization** should be the method of choice.

Some products cannot withstand the temperature conditions of autoclaving, the ingredients may be heat labile, or the package may be physically affected by the pressure changes (e.g., prefilled syringes), and **aseptic processing may then be necessary.**

References

Bunn, G. P. (Ed.). (2015). *Good manufacturing practices for pharmaceuticals* (7th ed.). John Wiley & Sons.