Risk Analysis and Process Validation

A. Hamid Mollah

Process validation is required by the current good manufacturing practice (cGMP) regulations for finished pharmaceuticals (1). The FDA’s initiative in pharmaceutical GMPs for the 21st Century is a science- and risk-based approach to product quality regulation incorporating an integration of quality systems. The risk-based approach should enhance industry’s ability to focus on identifying and controlling critical factors that affect process and product quality. The International Conference on Harmonisation’s (ICH’s) Q7A GMP guidance for active pharmaceutical ingredients (APIs) requires validation of critical processing steps determined to affect API quality and purity (2). To have a successful process validation, it is imperative to determine critical processing steps and critical parameters. Risk analysis assists in identifying those steps along with the critical factors and/or parameters that affect product quality. A documented risk analysis of a manufacturing process will assist in process validation. For the purpose of illustration, I’m applying risk analysis to APIs; however, the concept can be applied to other products as well.

DEFINITIONS

The FDA defines process validation (PV) as establishing documented evidence to provide a high degree of assurance that a specific process will consistently produce a product meeting predetermined specifications and quality characteristics (3). The ICH defines it as documented evidence that a process, operated within established parameters, can perform reproducibly and effectively to produce an intermediate or API meeting predetermined specifications and quality attributes (2). The ICH Q7A definition of critical refers to process steps, conditions, test requirements, or other relevant parameters or items that must be controlled within predetermined criteria to ensure that an API meets its specification (2).

Critical Control Parameters: Critical parameters and/or attributes are normally identified during development or from historical data — along with ranges necessary for reproducible operations. Critical limits should not be confused with operational limits. In-process and release (end product) parameters are controlled and monitored during production. Some noncritical process parameters are also controlled and monitored to reduce variability and operator error in GMP operations. All controlled process parameters can be divided into two categories: critical controls and operational controls. Those established to protect product quality are critical control parameters. Those monitored and controlled during GMP production, but with no established evidence of product quality impact, are operational control parameters.

PROCESS VALIDATION FOR API MANUFACTURING

A series of qualification and/or validation activities take place after commissioning of a facility, its equipment and utilities. Routine qualification activities include design (DQ), installation (IQ), qualification (OQ), and performance qualification (PQ). User requirements specifications (URS), functional specifications (FS), and design specifications (DS) documents are used in design qualification. Before PV begins, the associated equipment, utilities, and control systems must be qualified. PV is the final step before declaring a manufacturing process to be validated. PV data are usually presented to the regulatory agency during application submission. Therefore, they are critical to regulatory approval. Regulatory input on PV along the way can speed up the approval process.
A Modular Approach: Because of the complexity of the manufacturing process, a modular approach is routinely used in API manufacturing. The entire process is divided into several steps (modules) based on distinct process inputs and outputs. Figure 1 is a flow diagram of API manufacturing and process validation modules. Output of any particular module will provide the input (feed) of the subsequent module. Hence, successful conformance runs require meeting all acceptance criteria for each module. Protocols must be developed and approved for all process validation activities. The “Protocol Development” box lists considerations for a manufacturing process using qualified equipment, facilities, utilities, and control systems.

RISK ANALYSIS TOOLS
The types of risks a pharmaceutical company must deal with include patient risk (safety and efficacy of the drug), operational risk (operation safety, contaminations, or process variability), financial risk (product loss, reputation, and legal costs), and regulatory risk (FDA 483s, warning letters, product recalls, seizures, even legal actions). Taking those risks into consideration is an integral part of developing a manufacturing process. Risk analysis in PV promises to minimize the process risk. Risk assessment tools help in defining the process and identifying critical areas and/or steps in that process, areas of risk and/or hazard, and critical control points. Performing risk assessment of scale-up and/or manufacturing process is recommended as well.

Among the risk analysis tools available, fault tree analysis (FTA) and failure mode and effect analysis (FMEA) are both used in the medical device industry (4). Hazard analysis and critical control points (HACCP) are used in the fisheries industry (5). The World Health Organization (WHO) published in an expert committee report an annex titled “Application of Hazard Analysis and Critical Control Point (HACCP) Methodology to Pharmaceuticals” (6).

Fault Tree Analysis (FTA): FTA is a deductive, top-down approach to failure mode analysis (7). First, a system failure or safety hazard is assumed. Then, the combination of conditions required for that event (or failure) to occur is systematically defined, usually by identifying how failure-related events at higher levels are caused by lower-level “primary events” (failure of an individual component) and “intermediate events” (failure of a subsystem). The resulting information is organized in the form of a “fault tree diagram,” with the top event first. Events at

- **Protocol Development Check List**

  Ensure that approved operating procedures are in place.
  
  Validate methods.
  
  Train and/or qualify operating personnel.
  
  Complete process description and flow diagram.
  
  Identify product quality attributes, and justify acceptance criteria. Review of risk analysis, process development runs, clinical manufacturing, and license and in-house specifications for an existing process will assist in identifying product quality attributes and their acceptance criteria.
  
  Determine process variability. Various methods used include statistics (manufacturing and clinical data sets are not significantly different); historical trends (all data from manufacturing scale runs are within historic range of clinical manufacturing data); and “mean ± 3SD” (data from manufacturing scale runs are within mean ± 3 standard deviations of the clinical data).
  
  Perform at least three process validation conformance runs. Additional runs may be required for verification of some critical parameters.
  
  For manufacturing processes, make validation maintenance an ongoing activity.

![Calibration Manager 4](https://example.com/calibration-manager-4.png)
different levels of the tree are connected by logic gates defined by Boolean logic ("and/or" gates, for example). The tree directly points to the root cause of an event (or failure) along with other contributing events at all levels within the scope of the analysis.

Sometimes certain events may need to occur together for the top event to occur. In such cases, those events would be arranged under an "and" gate, meaning that all the basic events listed would need to occur to trigger the top event. If the basic events alone would trigger the top event, then they would be grouped under an "or" gate. The entire system — as well as human interactions — would be analyzed when performing FTA. Figure 2 shows an analysis for microbial contamination in a fermentation processes.

**Failure Mode and Effect Analysis (FMEA)** is a preventive, bottom-up approach to identifying all potential failures of a product, process, or system before use. It is also used to assess the effects or consequences of identified failure modes (8). A cross-functional team would prepare an FMEA to evaluate products and manufacturing processes and ensure they are designed to meet customer expectations. Note that failure mode and effect criticality analysis (FMECA) considers the importance (criticality) of identified failure modes with respect to safety, successful completion of a system’s mission, or other criteria.

The purpose of FMEA is to identify and possibly remove probable failure modes during process and/or system design. Use of FMEA typically begins in the early stages of product and/or system development. The FMEA progresses over time along with changes in the product/system, design and accumulation of information about performance in preproduction testing, and filed experience. FMEA is a practical, detailed tool for analyzing major areas identified by FTA. Table 1 shows an FMEA process for microbial contamination, not including ratings (risk numbers).

**HACCP** is a systematic approach to analyzing a process, determining high-risk steps, and controlling or monitoring those steps to thereby ensure that the process will always yield quality product (5). HACCP provides detail and documentation proving that a company understands its product and process well enough to control or monitor parameters important to the manufacture of quality products.

HACCP involves the following steps or principles:

- Conduct a hazard analysis (Principle 1).
- Determine the critical control points (Principle 2).
- Establish critical limits (Principle 3).
- Establish monitoring procedures (Principle 4).
- Establish corrective actions (Principle 5).
- Establish verification procedures (Principle 6).
- Establish recordkeeping and documentation procedures (Principle 7).

### HACCP IN DETAIL

When applying the cGMP regulations in pharmaceutical manufacturing, we in fact comply with numerous HACCP principles already. HACCP plan development includes identifying the members of an HACCP team, assigning responsibilities, creating a product description (distribution, intended use, consumers, and so on), and developing a process flow diagram.

**HACCP Principle 1:** Conduct a hazard analysis. A *hazard* is defined as a biological, chemical, or physical agent that is reasonably likely to cause

<table>
<thead>
<tr>
<th>Step</th>
<th>Potential Hazard</th>
<th>Justification</th>
<th>Hazard Addressed in the Plan?</th>
<th>Control Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioreactor steam-in-place (SIP)</td>
<td>Inadequate microbial kill</td>
<td>Bioburden growth will contaminate the bioreactor</td>
<td>Yes</td>
<td>SIP process</td>
</tr>
<tr>
<td>Working cell bank (WCB) vial thaw</td>
<td>Thaw temperature and time</td>
<td>Thaw at warm temperature, not exceeding maximum temperature and time specified</td>
<td>No</td>
<td>Operator verification, SOP to control thaw temperature and time, and system calibration</td>
</tr>
</tbody>
</table>

**Table 2: Hazard analysis for a bioreactor SIP and vial-thawing process**

<table>
<thead>
<tr>
<th>Step</th>
<th>Hazard Addressed in the Plan?</th>
<th>Control Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermentation</td>
<td></td>
<td></td>
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</table>

**Table 1: Failure mode and effect analysis (FMEA)**

| System Description: Microbial Contamination in a Bioreactor | References: | Complied by: | Date: | Reviewed by: |

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</tr>
</thead>
<tbody>
<tr>
<td>Fermentation</td>
<td>Aseptic condition</td>
<td>Microbial contamination</td>
<td>Product discard</td>
<td>Inadequate SIP Inoculation Media feed Sampling Ineffective CIP</td>
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</table>
illness or injury if not controlled. The likelihood of a hazard should be judged in the absence of controls. For pharmaceutical application, the definition of hazard should be expanded to include the danger of a product failing to meet its quality attributes and thus being likely to harm patients. Table 2 displays a hazard analysis for a bioreactor steam-in-place (SIP) and working cell bank (WCB) vial-thawing process.

**HACCP Principle 2:** Determine the critical control points (CCPs) at which control can be applied and is essential to prevent or eliminate hazards or reduce them to acceptable levels. Each step in a manufacturing process comprises individual actions or variables; not every action within a step is a CCP. The task here is to narrow those down to the minimum number required to control a process and prevent hazards. The following factors are considered in determining CCP:

- Controlling a subsequent process step may be more effective for controlling a hazard, so it may be the preferred CCP.
- More than one step in a process can be involved in controlling a hazard.
- More than one hazard may be controlled by a single control measure.

For example, any contamination in a bioreactor will lead to nonaxenic operations. Therefore, it is crucial to validate a successful SIP process in which saturated steam of a certain temperature is supplied in the bioreactor for a certain amount of time. So bioreactor SIP qualifies as a CCP.

**HACCP Principle 3:** Establish critical limits. Each CCP must have an assigned limit. Whenever that limit is exceeded, a corrective action (Principle 5) will be documented. Usually, critical limits are different from operational limits. Critical limits must be attainable, accurate, robust, and scientifically based. For example, the critical limits for a bioreactor SIP critical control point are temperature (expressed in Fahrenheit or centigrade degrees), time, and steam quality (dry or moist).

**HACCP Principle 4:** Establish monitoring procedures to indicate a state of control, and provide written documentation for use in verification. Continuous monitoring is preferred whenever feasible. If monitoring indicates a trend toward loss of control, then action(s) can be taken to bring the process back into control before any deviation from the critical limits occurs. Among other factors, real-time monitoring includes...
visual observation and temperature, pH, and conductivity levels. Bioburden testing and other delayed results can be used for verification.

**HACCP Principle 5:** Establish corrective actions. An important purpose of corrective actions is to prevent hazardous products from reaching consumers (9). Wherever a deviation from established critical limits occurs, corrective actions are necessary. Such actions should include the following elements:

- Determine and correct the cause of noncompliance.
- Determine the disposition of noncompliant product.
- Record the corrective actions that have been taken.

Once hazards, CCPs, and limits are known, asking and answering the question, “What will be done if this limit is exceeded?” (and implementing that answer into a procedure) dramatically streamlines the corrective action process. If a critical limit is exceeded, the decision about what to do is already defined, and the disposition of the product is predetermined. The investigation can concentrate on how it happened.

**HACCP Principle 6:** Establish verification procedures. Verification is defined to include those activities, other than monitoring, that determine the validity of an HACCP plan and that the system is operating according to that plan. One aspect is evaluating whether the facility’s HACCP system is functioning according to the plan. An effective HACCP system requires little end-product testing because sufficient validated safeguards are built in the process early on.

**HACCP Principle 7:** Establish recordkeeping and documentation procedures. Any weakness in recordkeeping indicates fundamental problems with the quality system. Recordkeeping is the foundation for all regulatory requirements: “It was not done if it was not recorded.” For a manufacturing company, however, the documentation in itself is not the product to be sold; it is a means to ensure quality of that product.

**Benefits of Risk Analysis**

Use of a particular tool will depend on a company’s in-house expertise. Any of the tools described herein (FTA, FMEA and HACCP) can be used alone or in combination. FTA is a top-down approach to failure and safety analysis. A fault tree shows a failure’s root cause. FMEA is a bottom-up approach to identify failures and their consequences. It begins at the design stage and evolves with time. HACCP is a proven system-based approach used in other industries and recommended by WHO for pharmaceutical manufacturers.

The term *hazard* is used in food to signify safety concerns. To realize the full benefit of HACCP, the word can be used for both safety and quality concerns in the pharmaceutical industry, where quality issues lead to noncompliance, safety concerns, and business risks. Clinical trial departments conduct product safety and efficacy studies. The manufacturing department is concerned with making a high-quality product that meets predetermined quality attributes. Business loss due to product rejection as a result of in-process testing is not considered a hazard in...
Life Cycle Approach in PV

Product quality and purity are continuously monitored through in-process testing and release testing of the end product. Trending data, deviations, and change controls are reviewed by management in its annual product review. Process changes are reported to the agencies through prior approval supplements (PASs), changes being effected (CBE) documents, and annual reports. A product–life-cycle approach in PV will organize and verify major activities that occur during the life of a product. This approach starts at PV planning and ends with product discontinuation. The cycle is based on ISO 9001 requirements: a plan–do–check–act (PDCA) cycle. Activities that are conducted, reviewed, or verified at various steps are listed in the “PDCA” box.

PV is a regulatory expectation. Applying risk analysis to PV will meet regulatory expectations by identifying, controlling, and documenting critical steps, actions, and parameters. The life-cycle approach to PV organizes and verifies major activities that occur throughout the life of a product. Using this approach can result in numerous benefits such as creating process expert teams, rapidly resolving process deviations, determining trends toward loss of control, complying with regulatory requirements, assessing the impact of process changes, and identifying areas of process improvement.

REFERENCES


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