Stage 3 Process Validation and the Role of Quality Risk Management

Ranjani Prabhakara, PhD
Center for Drug Evaluation & Research
Office of Compliance
Office of Manufacturing Quality

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Today’s Presentation

Breakdown of what OMQ Does

Process validation regulations

FDA Guidance: Process Validation and ICH Q9

Case Studies

- Process variation
- Raw materials
- Facilities and equipment

OC mission & vision

**Mission:** to promote and protect public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.

**Vision:** through excellence in risk- and science-based policy, surveillance, and enforcement, we prevent consumer exposure to unnecessary risk from drugs throughout their lifecycle.

Source: FDA

www.fda.gov
What OMQ does

- We evaluate compliance with Current Good Manufacturing Practice (CGMP) for drugs based on inspection reports and evidence gathered by FDA investigators.
- We develop and implement compliance policy and take advisory actions to protect the public from adulterated drugs in the U.S. market.

Source: FDA

How Cases Come to OMQ

- OMQ evaluates cases related to human drug facilities with deficient CGMP
  - About 10% of the CGMP inspectional “universe” (~5% with FDA action)
- Cases can be generated internally by OMQ
  - For example, informants and for-cause assignments
- Case referrals can come from ORA and from other FDA offices and centers:
  - Office of Pharmaceutical Quality (including OPF and OS)
  - Other Compliance sub-offices
  - Other FDA Centers (usually other compliance offices)
William Edwards Deming on quality

“Uncontrolled variation is the enemy of quality.”

“It is not the fault of the worker, it is the fault of the system.”

Process Validation Guidance

*Process Validation: General Principles and Practices*

- Uses a *lifecycle* concept
- Three stages that link:
  - Product/process development
  - Qualification of commercial manufacturing
  - Maintenance of process state of control
- Contributes to *drug quality*
- FDA Guidance document is online at: [https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070336.pdf](https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070336.pdf)
Variation and Drug Quality

• Successful process validation:
  “...is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes.”

• Understanding variation (the enemy of control)
  – Sources
  – Detection
  – Impact
  – Controlled in a manner commensurate with risk

Process Validation: Lifecycle Stages

<table>
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<tr>
<th>Description of Activities</th>
<th>Goals</th>
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<td><strong>Stage 1: Process Design</strong></td>
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<tr>
<td>Lab, pilot, small scale and commercial scale studies to establish process based on knowledge</td>
<td>Functional understanding between parameters (material and process) and quality attributes</td>
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<tr>
<td><strong>Stage 2: Process Qualification</strong></td>
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| ▪ Facility, utilities and equipment  
▪ Performance Qualification (Confirm commercial process design) | Scientific measurable evidence that  
▪ product meets specifications consistently and  
▪ process performance meets acceptance criteria; reproducible |
| **Stage 3: Continued Process Verification** | |
| ▪ Monitor, collect information, assess during commercialization  
▪ Maintenance, continuous verification, process improvement | Maintain or improve control and reduction in product and process variability |
Stage 3: Continued Process Verification

• Description of Process Validation Stage 3 activities:
  – “Ongoing” assurance is gained during routine production that the process remains in a state of control.”
    • State of control = The validated state
    • Knowledge gained during commercial manufacturing
    • Need a strong degree of detectability for undesired process variability throughout processing
    • CGMP requirement (§ 211.180(e), § 211.110)
    • Statistical assurance of a stable process has been problematic for the pharmaceutical industry

Stage 3: Detect Variation

• Timely assessment; don’t wait for FDA
  • complaints/returns  • OOS and OOT findings  • deviation reports
  • process yield variations  • batch records  • incoming raw material records
  • adverse event reports  • Etc.

• Have quality unit and production staff meet periodically to discuss:
  – Operator feedback on process performance
  – Trends
  – Undesirable process variation
  – CAPAs
Stage 3: Detection of Risk Over Time

• What happens during commercial manufacturing?
• Perform activities to continually assure the process remains in a state of control.

Quality Risk Management (ICH Q9)

• “Systematic processes designed to coordinate, facilitate, and improve science-based decision making with respect to risk to quality.”

• Risk to drug quality is a major focus of Q9
  – “maintained throughout the product lifecycle…”
  – “attributes that are important to the quality of the drug product remain consistent…”

• Guidance online at: www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf
Q9 - Quality Risk Management

Two primary principles of quality risk management are:

• The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

• The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

Three Questions to Assess Risk

• What *might* go wrong?
• What is the *likelihood* (probability) it will go wrong?
• What are the *consequences* (severity)?
  – ICH Q9 section 4.3
Q9 and Stage 3 Process Validation

• Commensurate with risk
• Executive oversight is critical
• Poor design or poor execution at any step poses a risk to product, such as:
  – Contamination (microbial, chemical, physical, etc.)
  – Decreased potency, stability, etc.
• Evaluation and response to risks should ultimately link to protection of the patient
  – All drugs should be of high quality
  – Use of statistical tools to evaluate process control and risk

Use of Statistical Tools

• Process Validation Guidance:
  We recommend that the manufacturer use quantitative, statistical methods whenever appropriate and feasible. Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e).
• Examples from ICH Q9:
  – Design of experiments
  – Histograms
  – Pareto charts
  – Control charts
  – Process capability analysis
Recurrent CGMP issues 2015-2017

Sterile drugs:
- Particulates in sterile injectables
- Media fills – inadequate investigations and procedures
- RABS and isolators, proper use/function

Drug substances:
- OOS investigations
- Change management

Other major issues:
- Raw material qualification and testing
- Microbiological control, including bioburden and cleaning issues
- Disinfectant efficacy
- Environmental monitoring procedures and investigations

Case Study 1 – Process
Sterile pediatric oncology drug manufacturer
Case Study 1 - Process

• Product A had multiple OOS events for various particulates and other impurities
  — *Your quality control unit identified particulate matter in several batches...*

• Particles and other impurities included:
  — Stopper-related metal particulates
  — Unidentified fibers
  — Particles from a botanical source
  — Aggregates
  — Conformational protein variants

Case Study 1 – Relevant Guidance

• Process Validation Guidance Section IV.D:
  — Periodic meeting of quality unit with production staff to evaluate data, discuss possible trends or undesirable process
  — Firm may need to improve/optimize the process by altering some aspect of the process or product

• Q9 Annex II.3:
  — Decrease variability of quality attributes (i.e., product and manufacturing defects)

• Q9 Annex II.7:
  — Root cause and CAPA identification during OOS investigations
Case Study 1 – Process Verification

- Questions to ask:
  - How has the facility drifted from the validated state?
  - What changed during that time?
  - Are implemented CAPAs effective in maintaining the validated state?

- Systems for detecting control:
  - Visual inspection
  - Bioburden analysis
  - Biological assay
  - Sterility and endotoxin testing
  - Stability testing
  - Statistically sound sampling plans

- Relevant trends:
  - Increased OOS events for particulates and impurities

Case Study 1 – Risk Assessment

- What might go wrong?
  - Microbiological and/or particulate contamination of the finished drug product

- What is the likelihood (probability) it will go wrong?
  - Likely, due to a poorly controlled process combined with inadequate investigations and CAPAs

- What are the consequences (severity)?
  - Potentially severe or life-threatening
  - Particles may enter capillaries in lungs
  - Microbiological contamination could result in sepsis
  - Pediatric indication and immunocompromised patient population
Case Study 2 - Raw Materials

Manufacturer of biotech-derived drug substance, aseptically filled drugs, and solid oral dosage drugs

Case Study 2
Three Examples: Critical Role of Raw Materials

- **Raw Material 1** – used in biologic, two finished lots with OOS endotoxin
  - Raw material promoted growth
  - Its specification was too high (cumulative effect unknown at BLA filing)
  - Lot was rejected, but this led to a drug shortage

- **Raw Material 2** – industrial (not pharmaceutical) material used in Product B
  - Analysis identified unknown impurities in raw material
  - One lot contained chemical hauled in non-dedicated tanker (change in supplier)
  - Investigation did not cover all lots manufactured with the industrial-grade material

- **Raw Material 3** – used in more than 100 lots of Product C, contaminated with Raw Material 4
  - Contaminated lot received
  - Potential impact on stability due to degradation or interactions
  - No analytical method to monitor contaminant over the product shelf life
Case Study 2 – Relevant Guidance

• Process Validation Guidance Section IV.D
  – Analysis of product and process data related to product quality
  – Evaluation of data related to incoming material quality and qualification of suppliers
  – Requirement under 21 CFR 211.180(e)

• Q9 Annex II.5
  – Evaluation of suppliers and contract manufacturers
  – Starting materials and possible quality risks from variability
  – Adequacy of storage and transport conditions

Case Study 2 – Process Verification

• Questions to ask
  – When did the process drift from the validated state?
  – What changed during that time?
  – Is this a trend or an individual event? ➔ Investigation

• Systems for detecting control
  – Endotoxin testing
  – Impurities testing (HPLC)
  – Stability testing
  – Retain sample testing
  – Statistically sound sampling plans

• Relevant trends
  – High endotoxin levels (finished product vs. raw materials)
  – Unidentified peaks in multiple batches
Case Study 2 – Risk Assessment

• What might go wrong?
  – Intravenous injectable drug with high endotoxin (2A)
  – Unknown chemical contaminants (2B)
  – Impact on stability (potency) of final drug product (2C)

• What is the likelihood (probability) it will go wrong?
  – Impact to multiple lots and supplier qualification issues make it more likely something will go wrong (2A – C)
  – Can’t test for things you don’t know to test for (2B)

• What are the consequences (severity)?
  – Potentially fatal sepsis or endotoxic shock (2A)
  – Potentially severe depending on the nature of a chemical contaminant (2B)
  – Potential decrease in potency may impact clinical outcome (2C)

Case Study 3 – Facilities

Manufacturer of multiple sterile oncology drugs and sterile API
Case Study 3 - Facilities

• Aseptic filling suite had tiled floors with visible filth in the seams, cracks, and other damage
  – *Floors should be seamless where sterile products are manufactured.* Smooth, hard surfaces that are easy to clean prevent accumulation of filth and discourage microbiological growth.

• Stagnant water was present under the filling machine
  – *Stagnant water is a potential source of microbiological contamination, including biofilms and other filth.*

• Firm used damaged plates for EM
  – Agar was desiccated, cracked, or damaged.

Floor and Water Issues

Discoloration and unreachable stagnant water under filling machine

Unsealed seams

“Negative” EM plates
Case Study 3 – Relevant Guidance

- Process Validation Guidance Section IV.D
  - Qualification status (i.e. the state of control) should be maintained by monitoring and maintenance
  - Need periodic reassessment to determine if requalification is required

- Q9 Annex II.4
  - Appropriateness of facility for minimizing contamination
  - Environmental controls
  - Qualification of facilities

Case Study 3 – Process Verification

- Questions to ask
  - How has the facility drifted from the validated state?
  - What changed during that time?
  - Are implemented CAPAs effective in returning to the validated state?

- Systems for detecting control
  - Media fills
  - Bioburden analysis
  - Sterility and endotoxin testing
  - Retain sample testing
  - Statistically sound sampling plans

- Relevant trends
  - Numerous media fill failures
  - Bioburden and endotoxin OOS results
Case Study 3 – Risk Assessment

• What might go wrong?
  – Microbiological contamination of the finished drug product
  – Bacterial biofilms may lead to recurrent contamination
  – Micro false negatives

• What is the likelihood (probability) it will go wrong?
  – Between facility conditions and a lack of adequate microbiological testing, chances are higher

• What are the consequences (severity)?
  – Potentially severe or life-threatening
  – Potential for microbiological contamination of sterile injectable drugs
  – Vulnerable patient population

Matthew McMenamin, GSK 2015
Benefits

- Reduces process errors
- Reduces employee errors
- Reduces rejected batches
- Reduces need for investigations
- Reduces FDA 483 observations
- Reduces recalls and shortages
- Improves drug product quality

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