Process Validation Guidelines

Report highlights| 23rd February 2018

Process validation is an important element of pharmaceutical quality system

*An effective system provides assurance of the **continued capability of processes and controls** to produce a **product of desired quality** and to identify **areas for continual improvement***

– ICH Harmonised Tripartite Guideline Pharmaceutical Development Q10

***Quality, safety and efficacy** must be **designed and built into the product**; quality cannot be inspected or tested into the product*

– WHO Guidelines on Validation

*Effective process validation contributes **significantly to assuring drug quality;** Quality cannot be adequately assured merely by in-process and finished-product inspection or testing*

– FDA: Process Validation: General Principles & Practices

*Process validation should not be viewed as a one-off event. It incorporates a **lifecycle approach** linking **product and process development, validation of the commercial manufacturing process** and **maintenance of the process** in a state of control during **routine commercial production***

– EMA: Guideline on process validation for finished products

SOURCE: Excerpts from guidelines by regulatory agencies

Process validation is critical to ensure product quality, safety, delivery and cost

Quality and safety

Ensure patient safety

Quality, safety & efficacy is built into the product

Improve performance for legacy and new drugs

Delivery and cost

Minimum rejects & reworks

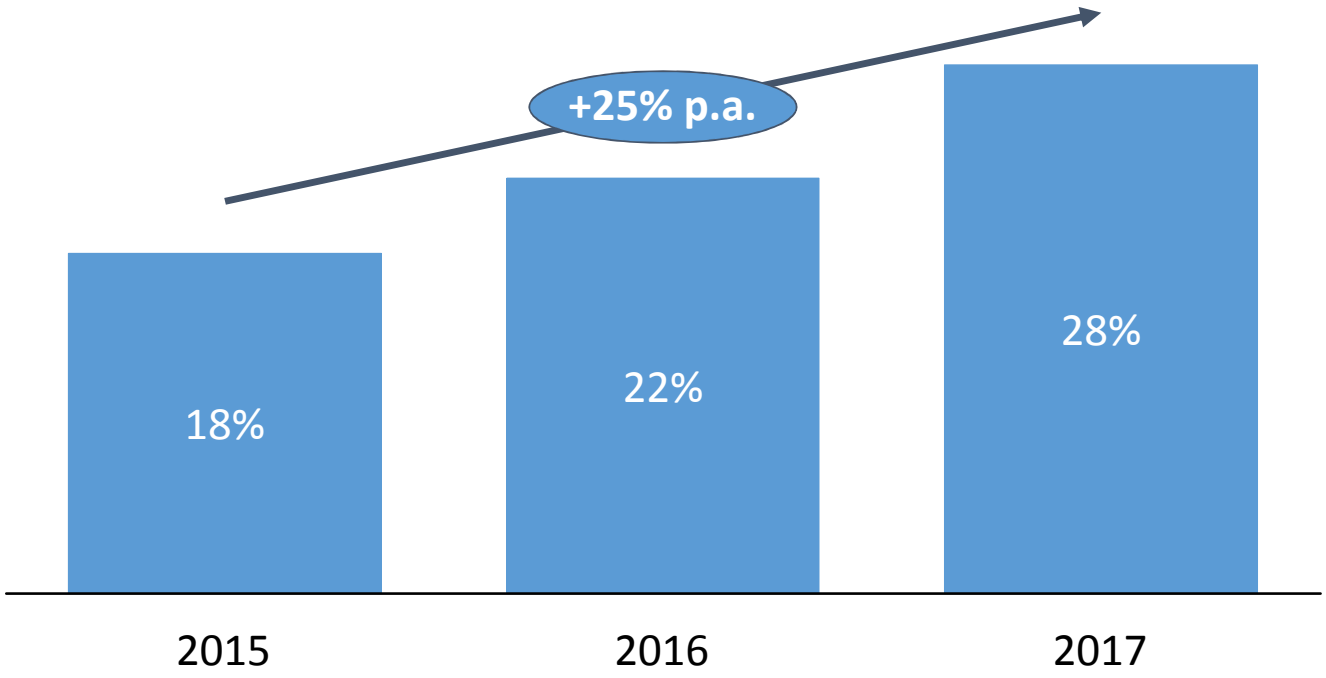
Reduce batch to batch variation

Reduce cost of lost sales & remediation

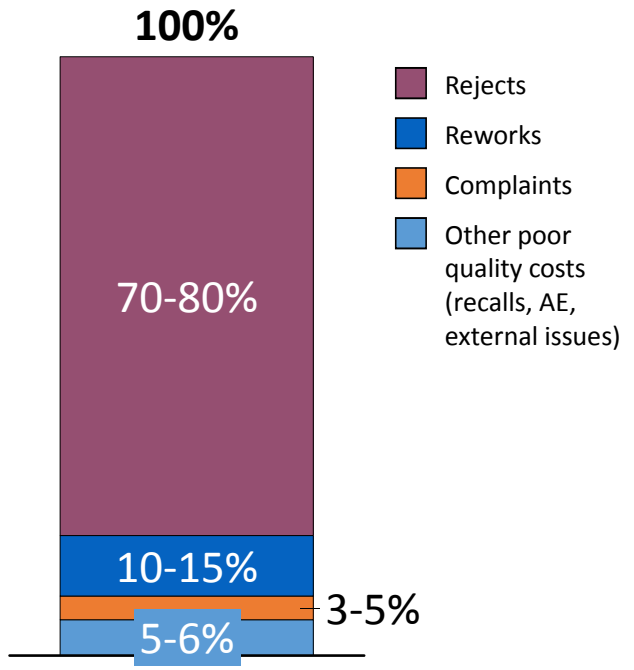
Product quality related investigations have been on the rise and contribute maximum to the cost of poor quality

One of the leading contributors to regulatory observations (FDA WL example)[1]

Approximate % of total observations on batch failure investigations



Major contributor to poor quality cost[2] (Indian pharma site example)



1 Analysis of FDA WL over the last 3 years

2 Poor Quality costs are costs related to rejects, reworks, complaints, adverse events, recalls and other related to production failure or external issues

Process validation guideline adopts the lifecycle approach and is designed for implementation in the Indian context

Lifecycle approach for process validation

Stage 1: Process design

Commercial manufacturing process defined based on knowledge gained through development & scale-up activities

Stage 2: Process qualification

Process design **evaluated to determine if it is capable of reproducible** commercial manufacture

Stage 3: Continuous process verification

Ongoing assurance gained during routine production that the process remains in a state of control

Each lifecycle stage covers the following elements

- **Detailed actionable steps** to execute the guidelines at shop floor
- **Harmonised and standardised guidances**, integrating all guidelines and SOPs of QF members
- **Templates and tools for risk assessment**, statistically defining number of batches
- **Specimen and targeted elements** of process qualification protocol
- **Sampling plans and strategies**, including packaging as a part of process validation

SOURCE: Process validation guidelines by IPA

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Process validation
Sub-group 2

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Multiple elements of the process validation guideline are unique and designed specifically for the Indian pharma industry

NON-EXHAUSTIVE

Stage 1: Process design

- Risk Assessment & Mitigation Plan
- Derive/define QTPP, CMA, CPP & CQA
- Product development with QbD approach
- Establish design space
- Impact analysis : Scalable & non – scalable parameter
- Pre validation batches i.e Scale up exhibit, or engineering batch

Stage 2: Process Qualification

- Risk assessment to derive no. of batches (earlier 1 or 3)
- # batches: Based on complexity of the product and process
- Unit operation wise – testing plan
- PPQ protocol specimen
- Extensive sampling plan
- Define alert/ control limit
- Validation batch failure criteria and action plan

Stage 3: Continuous process verification

- Decision trees for any change in product lifecycle
- Change specific assessment criteria defined through flow chart
- Verification of new and legacy products
- Packaging Validation

SOURCE: Process validation guidelines by IPA

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Guideline includes detailing of outcomes required from Stage 1 for transition to Stage 2

Build process knowledge

- Early process design experiments to be conducted in accordance with sound scientific methods & principles
- **Design of Experiment (DOE)** helps develop process

Establish strategy

- Strategies designed to reduce input variation, or combine approaches
- Decisions regarding process controls aided by earlier risk assessments

Deliverables from Stage 1

- **25+ deliverables defined for stage 1 in guidelines, including:**

1. Critical Quality Attributes (CQAs)
2. Criticality and Risk Assessments
3. Quality Target Product Profile (QTPP)
4. Manufacturing Process Design
5. Process Validation Master Plan
6. Process Control Strategy

SOURCE: Process validation guidelines by IPA

2. Risk assessment specimen designed to capture product specific life cycle history

Elements to be covered

1. Formula
2. Process flow
3. CMAs of input materials (raw materials and packing materials)
4. Detailed Technical GAP analysis of equipment, unit operation wise
5. CPP – unit operation wise
6. Challenges faced and remedies at various stages (design to life cycle)
7. Deviation/OOS/OOT history
8. Learning and way forward

6. Elements of control strategy harmonized & standardised

All product quality attributes & process parameters (critical and non-critical) included

Raw material controls	**Performance parameters**	**Processing and hold time**
In-process and release specs	**Process parameter & ranges**	**Process analytical technology**
In-process controls	**Process monitoring**	

SOURCE: Process validation guidelines by IPA

Unit operation wise sampling methodology defined for PPQ studies

Sampling Strategy

- Extensive sampling plan (ASTM guideline E2709 & E2810) to demonstrate consistency
  - **Blend uniformity**
  - **Content uniformity**
- Process flow diagrams for assessment of uniformity
- Should include statistical rationale that underline the plan

Setting acceptance criteria and control limits

- Criteria for PPQ to be based on data available from Stage 1, prior knowledge and equipment capabilities
- Process of **individual product & process variable evaluation** defined
- **Acceptance criteria as per ASTM defined** includes:
  - Incoming material
  - Process parameters (CPP & KPP)
  - Attributes

SOURCE: Process validation guidelines by IPA

Key elements of CPV program detailed

NON-EXHAUSTIVE

CPV monitoring plan		• Outline **how various departments interact** and how information is compiled and reviewed • Comprehensive plan covering all elements, including roles and responsibilities, data analysis methods, sampling & criteria, etc.

Demon-strating CPV		• 2 primary sources of data:
		  • Process parameters
		  • Potential sources of variability
		  – Raw material quality
		  – Redundant equipment
		  – Personnel impact on process

Incorporating feedback from CPV		• **Communication of review outcomes** to manufacturing, quality, and regulatory stakeholders to modify the control strategy • **Frequency of data review to defined basis risk** • Annual commercial data compilation for **Annual Product review**

SOURCE: Process validation guidelines by IPA

Decision trees for validation studies & their batches for various changes in PLM defined

1. New products
2. Manufacturing site of product
3. Approved manufacturing process
4. Manufacturing process controls
5. Batch sizes
6. Equipment change
7. Capacity of an equipment
8. Source of API/Key RM
9. Specification of primary pack of finished product
10. Shape dimension of container
11. Approved pack size of finished product
12. PM which is not in direct contact with product
13. Vendor of PM
14. Primary packaging material of finished product
15. Qualitative/quantitative of composition secondary pack
16. Test procedure for primary PM & RM
17. Packing machine
18. Special features of packaging material
19. Secondary/tertiary packaging

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Benefits of having a robust process validation

1. Right At First Time
2. Improve Performance and reduce trial and error
3. Reduce Product Recall
4. Reduce Field Alert
5. Reduce Warning letters / 483's
6. Improvement in product conformance via scientific Risk based approach
7. Investigation cycle time reduction.