Process Validation Lifecycle Approach: A Return to Science

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Process Validation Event

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Program Summary

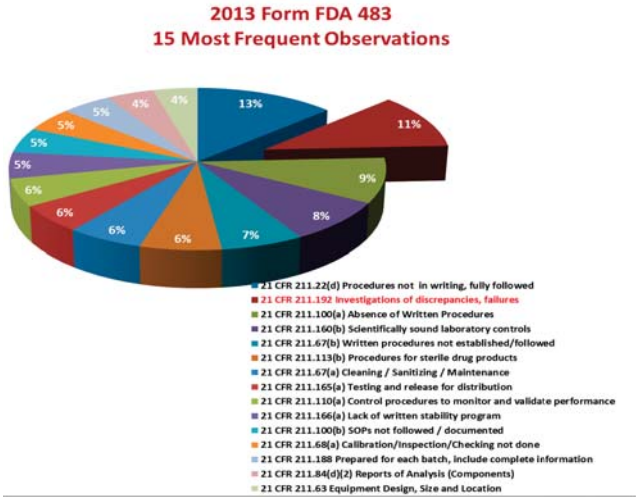
1. The expectations for process validation and process control have changed and are continuing to change – for the better.

2. More and more global health authorities and regulators are communicating their expectations for risk and science based justification for process control and validation approaches.

3. A true life cycle approach to process validation requires gathering useful, scientific information as process and control strategies are developed, thus saving time and resources during later qualification and validation stages.

4. The key is better understanding of the process, its sources of variation and their control, and the correlation between validation studies, sampling plans, process performance, product quality, and continued process verification.

How much manufacturing changed in the last 35 years?



The objective:

- Manufacture and distribute high quality, drug products and therapies that provide the best benefit the public.

The challenge:

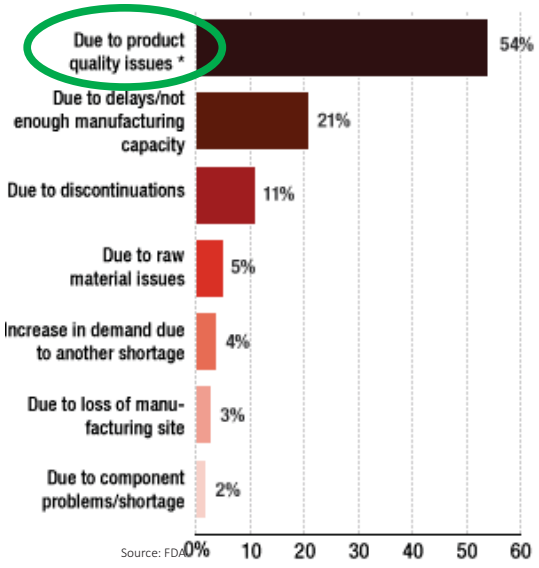
- Drug, biologic, and medical device products must be:

✓ Safe and effective
✓ Compliant with regulatory requirements
✓ Must also meet the three A's test
  - ➢ Available for use by the patient
  - ➢ Affordable
  - ➢ A reasonable business proposition

Healthcare topics in 2015

1. Drug Shortages
2. Drug Product Costs
3. Supply Chain integrity
4. Data Integrity
5. Innovative Therapies
6. Standardized Quality Metrics

Drug shortage reasons



- Foreign matter in filled product (particulates, fibers etc.)
- Microbial contaminations
- Glass breakage/container closure
- Mislabeling/incorrect product filling

A significant statement …

- In 2005, 61 drug shortages were reported to FDA, according to testimony at a 2011 congressional hearing. By 2010, shortages nearly tripled to 178, three-quarters of which were injectable drugs, which generally are made in smaller batches and are difficult to produce…

- …factors they cited were aging facilities, production lines crowded by manufacturers trying to produce various products, a lack of oversight over manufacturing subcontractors, and the economic downturn...

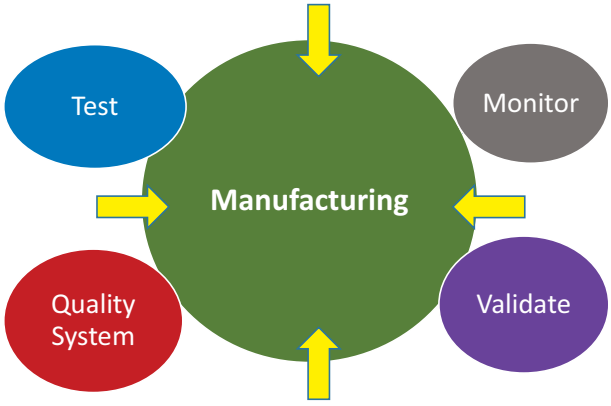
  - Clinical Pharmacology and Therapeutics
    Woodcock J, Wosinska M "Economic and technological drivers of generic sterile injectable drug shortages"

Reasons for lack of progress

- Inadequate process understanding
- Ineffective understanding of objective of validation
- Inadequate understanding of process risk
- Inadequate understanding of technology and science to mitigate risks
- Emphasis on speed to market
- Unaligned business models
- Failure to recognize unintended consequences of change
- Regulatory fears and barriers

A need for critical thinking

and focus on manufacturing science



Gemba (現場) means *actual place*. In manufacturing, the gemba is the production shop floor.

Points to consider …

1. Science, risk-based, critical thinking approaches

… to make decisions for evaluation, design, validation, operation and monitoring of drug manufacturing processes is essential for development and implementation of better process control strategies.

2. Technology

… should be considered and encouraged to reduce risks to product quality in manufacturing operations.

3. Partnership of manufacturers, regulators, and suppliers

… are the best way to ensure effective use of new technology.

4. New therapies and manufacturing approaches

… present challenges to existing and traditional methods for development, manufacture, validation and testing.

5. Global regulatory expectations

… requirements, guidance, and technical language/definitions should be consistent, where scientific evidence is agreed upon, is a way to reduce the redundant efforts and risk of misunderstanding.

Principles of lifecycle process validation can and should be used to improve the performance and control of existing processes.

Process improvement,
continually seeking to be better

Beware of common process control misconceptions

1. If something has not happened yet, it will likely not happen.
2. If something has not been cited during an inspection, it must be OK.
3. People related problems are the result of people making mistakes.
4. **(just) Complying with Health Authority regulations is enough to assure quality.**

The role of regulation and science

Manufacturers of drugs must assure that drugs will be safe and effective

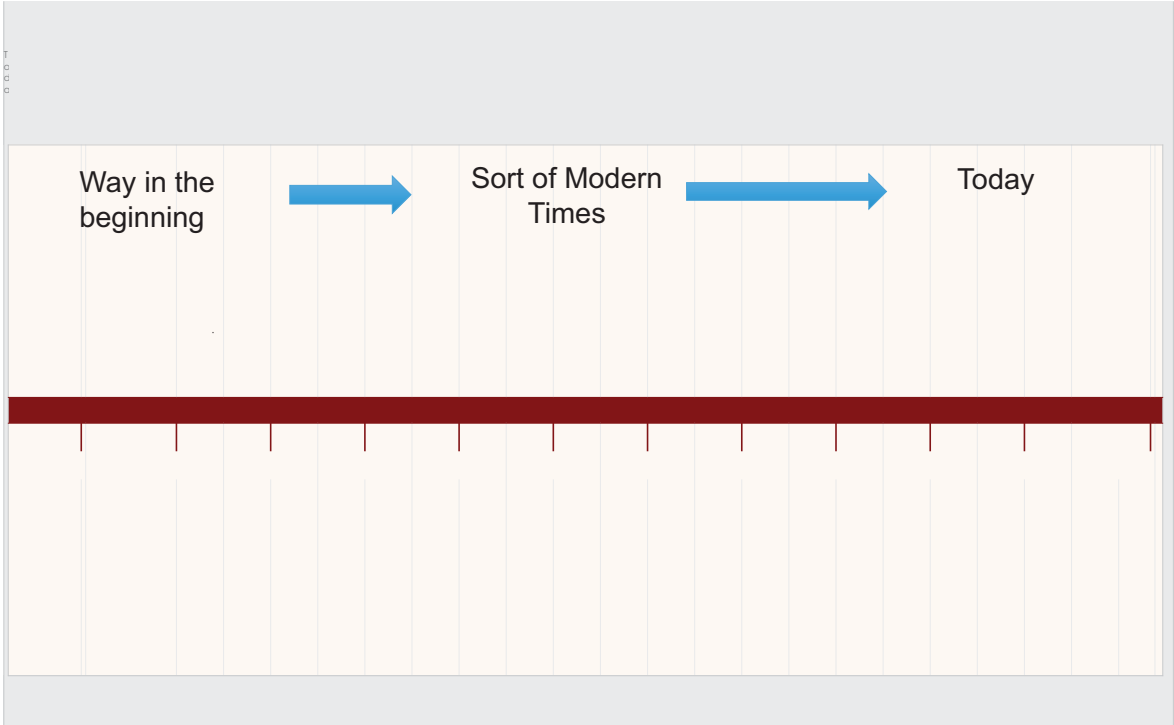
This is a moral, business, & legal obligation

Regulations are the "ticket" to the market place

Science makes the process effective

Process validation,
establishing and demonstrating process control

History of Process Validation



History of Process Validation

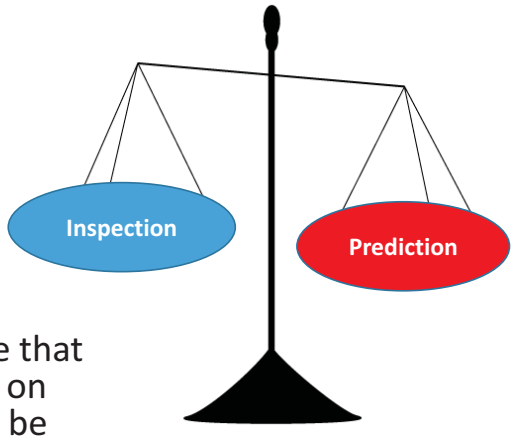
Product testing and assurance of patient safety

- 1970-71 outbreaks of *E. cloacae* and *Erwinia* contamination in LVP bottles
- Apparently caused by moisture seeping into a space under the screw cap of the bottles during cooling after sterilization
- Showed that testing and process monitoring was not enough to assure the quality of the product

21 CFR 211.100: **"There shall be written procedures for product and process control designed to assure that drug products have identity, strength, quality, and purity they purport or are represented to possess."**

Proving assurance is a balance of …

Observation and Prediction



Validation is prediction of outcome that cannot be fully observed, based on analysis of conditions which can be observed.

The wisdom of replicate runs

If you can do something
right three times,
you should be able to do it
that way always.

If running replicate batches validates the process, then why do process failures still occur?

Because stuff happens…

Stuff = **Process Variation**

Validation is a means to uncover process weaknesses:

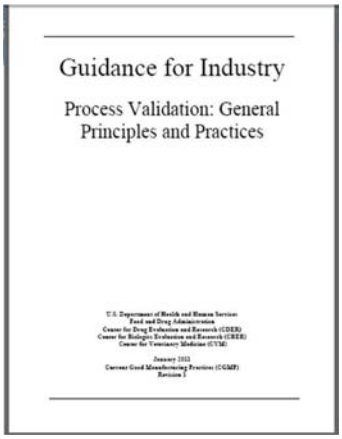
Sources of

VARIATION

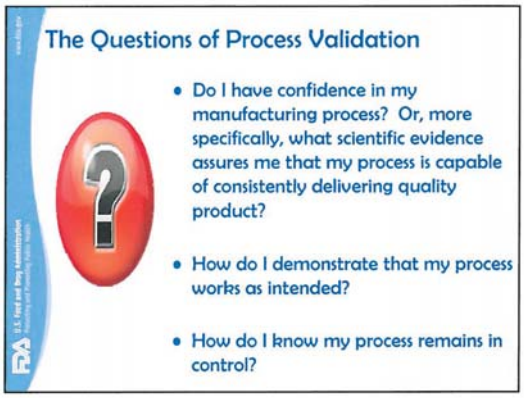
"No amount of experimentation can ever prove me right; a single experiment can prove me wrong.

- Albert Einstein

It's up to industry to decide how to validate


Guidance for Industry

Process Validation: General Principles and Practices



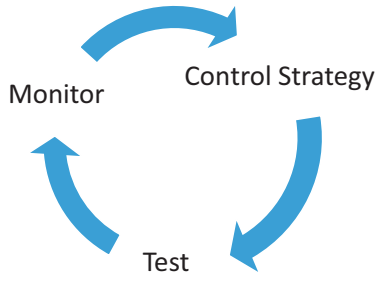
Process Validation Definition and Concept

- *Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.*
  - *'87 FDA Process Validation Guidance*
- defined process validations as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.
  - '11 revision to FDA Process Validation Guidance

Process Validation

When is the process validated?

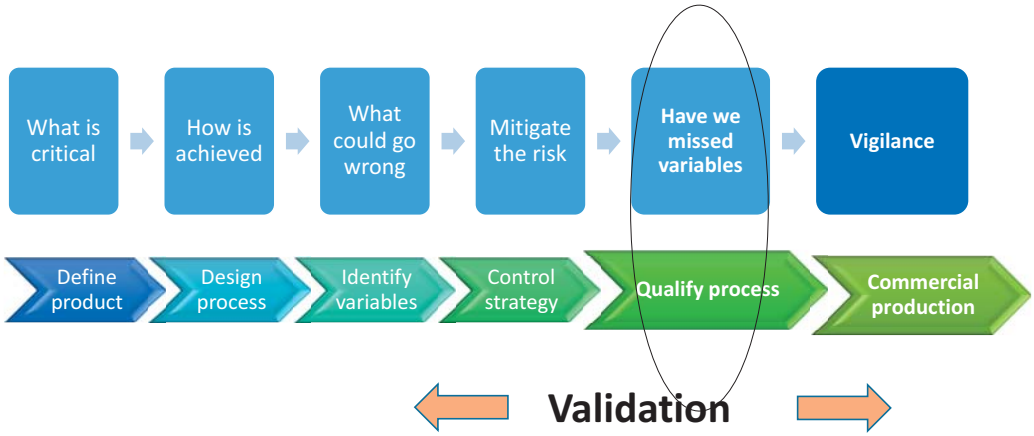
When are you confident the process is in control?



Stage 3
Continued or On-going Process Verification

Stage 2
Process Qualification

Process control and validation



Scientific interpretation of data

Process validation and the assurance of quality

A. Process Validation and Drug Quality

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

  - *FDA process validation guidance*

Process validation lifecycle approach

- Process validation should not be viewed as a one-off event. … 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 process validation submission guidance*

Ongoing Process Verification …

5.29. Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

5.30. The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.

5.32. Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.

- *Annex 15*

Process validation and process improvement

- The lifecycle concept links product and process development, qualification of the *commercial manufacturing process*, and maintenance of the process in a state of control during routine commercial production.
- This guidance supports process improvement and innovation through sound science. The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production.

  - *FDA process validation guidance*

10 key process validation points

1. Continuous process of evaluation, rather than an event
2. Understanding and controlling process variation is key
3. Process variables should be gleaned from process design
4. Process control assured through process design, not testing
5. Companies are already doing much of what is required
6. Articulate how efforts prove process is under control
7. The more done in early stages to understand process, the less needed later to confirm
8. Decisions should be based on scientific, statistically sound and risk based information
9. Facility and equipment must be qualified and shown to be reliable and suitable
10. Legacy processes also must be shown to be under control

Legacy process improvement

- Principles laid down in ICH Q8, Q9 and Q10 are applicable
- It is possible to perform a risk assessment and to introduce continuous process verification any time over the lifecycle on the product.
- Legacy products may benefit from historical data and experience gained
- In principle it is never 'Too Late'
  - EMA Guidance

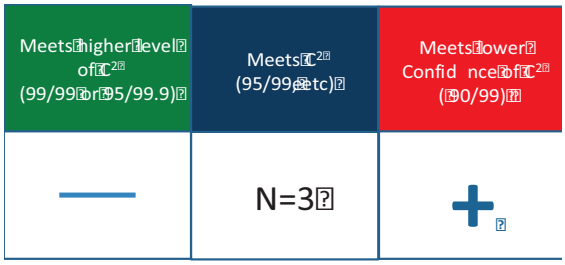
Number of batches

- Number of batches is not an acceptance criteria
- Results of data are the acceptance criteria, but batches provide the data
- Acceptance criteria aligned with objective of study, based on confidence you wish to achieve and the data you already have
- Statistical sampling is only one tool you have to provide confidence
- Prior knowledge, process robustness, and scientific principles

  may also be used

Confidence and coverage based on science, strategy, and statistics

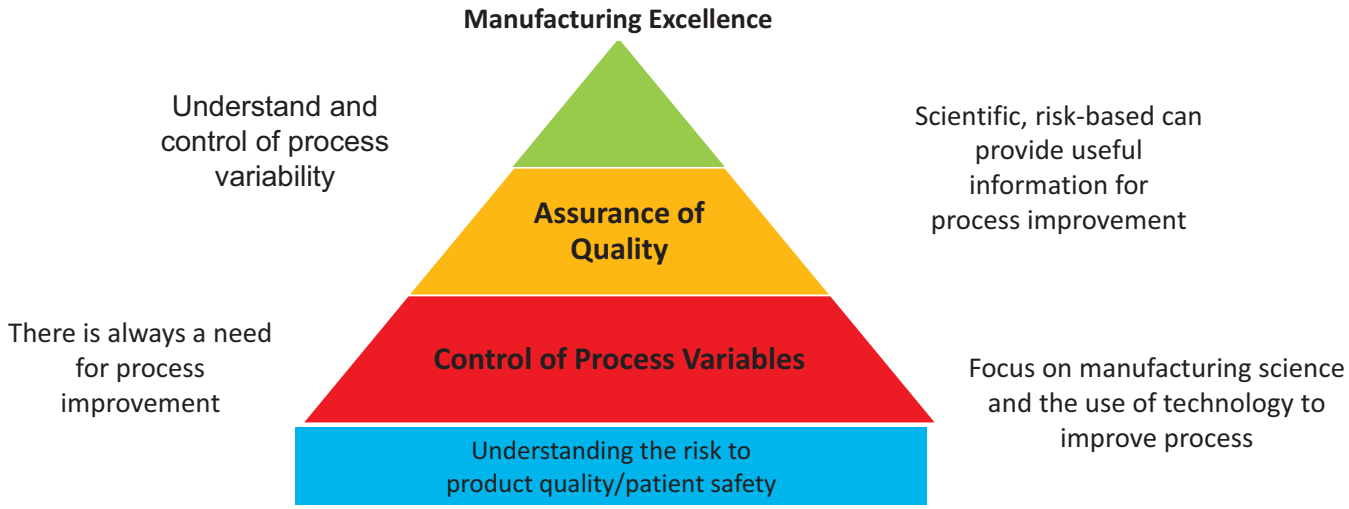
PPQ Batches



- Science gives us Severity, confidence and coverage
- Statistics gives us Occurrence rates
  - This helps us define the # of samples
- Strategy
  - This is a second level. We can increase /decrease based upon strategy. (Multiple trains, Tech Transfer)

CPV Risk Triage Table

Attribute Severity	Ppk < 1.0	1.0 ≤ Ppk < 1.5	Ppk > 1.5
High	Investigation	Investigation	SME and QA
Medium	Investigation	SME and QA	Close out By SME
Low	SME and QA	Close out By SME	Close out By SME



Thanks for your attention ….

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