# Implementing FDA & EMA Process Validation Guidance


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## Everything Old is New Again

- FDA's 2010 PV Guidance appears to be relatively new. Its cited origins are ICH Q8, Q9 & Q10. Its roots can actually be found in the mid-1980's.
  - Chapman, K. "The PAR Approach to Process Validation", *Pharmaceutical Technology*, Vol. 8, No. 12, pp 22-36, 1984.
  - Agalloco, J., "The Validation Life Cycle", *Journal of Parenteral Science and Technology*, Vol. 47, No. 3, p. 142-147, 1993.

## Where to Begin - Start at Stage 3!

**This may look wrong, but in the context of the Guidance it's not.**

- Currently marketed products represent the greatest patient, compliance & financial risk.
- Stage 1 & 2 will impact tomorrow's business, but Stage 3 is about today's!!

## Stage 3 & Corporate Risk

- Stages 1 & 2 are concerned with future products and not having a current approach that matches the guidance only impacts future products.
- Failure to have existing products adequately validated (using Stage 3 practices) imperils current operations. Products on the market must be fully compliant, and regulatory inspections are largely focused on approved products.

## FDA's Definition – 2011

- "For purposes of this guidance, *process validation is defined as the collection and evaluation of data, from the process design stage* ***through commercial production****, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process.*"

Emphasis Added

## FDA Implementation Advice

*"Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for legacy products and processes would likely* ***begin with the activities described in Stage 3."***

Emphasis Added

## There's Multiple Paths Ahead

**Existing Products**

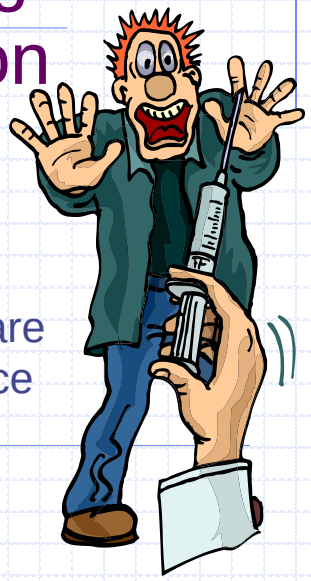
- Legacy products / processes should be screened for capability.
- Acceptable products should follow Stage 3 approaches
- Less capable product should be re-developed and progress through Stages 1 & 2.

**New Products**

- Those developed following the guidance (e.g., QbD and Stages 1 & 2)
- Transition through Stage 2½
- Followed by Stage 3 as defined in the guidance document

## Stage 3 – Existing Product Evaluation

Skip this for new products that are introduced following the guidance



## Stage 3 – Evaluation

- For existing products it is essential to assess past performance to establish whether the process/product is in a state of control:
  - If Cpk's are too low, redevelop the product / process (restart at Stage 1).
  - If CpK is OK >2, follow the Stage 3 expectations in the guidance.

## Making Silk Purses from Sow's Ears

- It really can't be done, processes must have reproducible outcomes (e.g., make product of consistent good quality) in order to be successfully produced and validated.
- The problem often lies in inadequate developmental efforts, and that's why doing Stage 1 properly is so important.
- Validation (per Stages 2 & 3) is only a means to keep score.

# Stage 1 – Process Design (aka Process Development)

## Development Timeline


| | | |
|---|---|---|
| **Pre-Clinical** | **Non-human studies** | **Pre-formulation** |
| **Phase I** | **Start to establish safety** | **Simple dosage forms** |
| **Phase IIa** | **Continue safety; start to establish single-dose efficacy** | **Simple dosage forms** |
| **Phase IIb** | **Establish multiple-dose efficacy** | **Start to develop/use commercial dosage forms** |
| **Phase III** | **Pivotal studies to support label claims** | **Commercial dosage forms** |
| **Phase IV** | **Additional claims; marketing studies; post-approval commitments** | **Commercial dosage forms** |

# Development & Validation

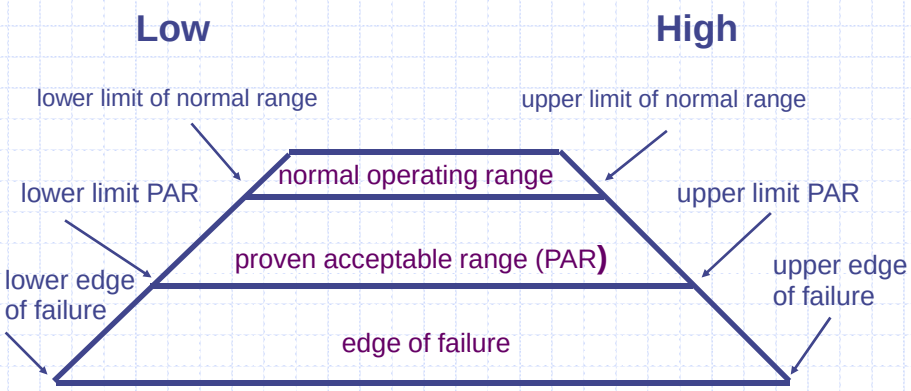
- "A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process. Manufacturers should:
  - understand the sources of variation
  - detect the presence and degree of variation
  - understand the impact of variation on the process and ultimately on product attributes
  - control the variation in a manner commensurate with the risk it represents to the process and product"

FDA Guidance

# Influence Matrix

| | IN-PROCESS AND FINAL PRODUCT CHARACTERISTICS | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PROCESS VARIABLES | G: Discharge characteristics | G: Granulation quality | G: Power load | D: Moisture content | S: Particle size distribution | S: Density | B: Flow properties | B: Density | B: Uniformity | F: Fill weight | F: Weight variation | P: Content uniformity | P: Dissolution |
| G: Batch size | S | S | S | ? | ? | ? | N | ? | ? | ? | ? | ? | N |
| G: Speed - main | W | M | S | N | W | W | N | N | N | N | N | N | N |
| G: Speed - chopper | M | W | W | N | W | W | N | W | N | N | N | W | W |
| G: Amount of water | S | S | M | S | S | S | S | S | W | S | S | W | S |
| G: Water addition rate | W | S | W | N | W | W | W | W | N | W | N | N | N |
| G: Granulating time | S | S | N | N | M | M | M | M | W | M | M | S | S |
| D: Initial temperature | | | | N | M | N | M | W | N | W | N | N | N |
| D: Drying temperature | | | | S | W | M | M | N | N | N | N | N | N |
| D: Air flow program | | | | S | W | M | N | N | N | N | N | N | N |
| D: Drying time | | | | S | W | M | M | N | M | M | N | N | M |
| S: Screen size | | | | | S | M | W | W | N | N | N | N | W |
| S: Feed rate | | | | | M | W | N | N | N | N | N | N | N |
| B: Loading | | | | | | | N | N | W | N | N | W | N |
| B: Speed | | | | | | | N | N | W | N | N | N | N |
| B: Blending time | | | | | | | N | N | S | N | N | S | N |
| F: Powder level | | | | | | | | | | S | S | N | N |
| F: Tamper settings | | | | | | | | | | S | S | N | W |

# PAR Approach to Validation

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# What's the Value of PAR Approach?

Which road is safer, and allows for faster speeds?

If the objective is to arrive on time and alive, which road should you take?

## Stage 1 - It's Backwards Again!!

- In risk management exercises, it's conventional to evaluate risk and then implement measures to mitigate it.
- In process development, we are expected to define risk mitigation measures effective on a commercial scale prior to having manufactured the product on that scale.
- We can't do that in a rigorous manner, but we should leverage prior knowledge with similar products & circumstances to the maximum extent possible.

## Stage 2 - Process Performance Qualification (aka) Product / Process Validation)

## Prerequisites

- Qualified process equipment & utilities.
- Validated analytical methods.
- Defined sampling methods.
- Established raw material, in-process and finished goods specifications.
- Written SOP's (drafts may be OK).
- Written, approved batch manufacturing instructions.
- Trained personnel.
- Approved PQ protocols.

## General Approach - 1

- Manufacture the process according to the defined manufacturing instructions.
- Have independent observer(s) present throughout the process.
- Observer documents validation activities.
- Independent monitoring may be used.
- All process parameters set at their defined set points.
  - "worst case" conditions are inappropriate

## General Approach – 2

- Monitoring & sampling must be non-intrusive to the process.
- Utilize expanded sampling throughout and all samples must be tested concurrently and considered in lot release decisions.
- Can be accomplished in a step-wise or unit operations oriented fashion.

## Process & Product Qualification

- The optimal approach to validation considers process parameters, product attributes and their relationship. Only in combination can a process/product validation be properly addressed.
- The optimal approach to validation considers process parameters, product attributes ***and*** the relationship between them.

  drying time --- moisture content
  mixing time --- content uniformity
  reaction conditions --- impurity levels
- The link between process parameters and product attributes is established during development.

# Transition from Stage 2 to Stage 3

## The Essential Questions

- The new guidance intentionally avoids being definitive about critical issues.

1. How much statistical confidence is enough?
2. How many lots are needed to complete Stage 2?

- The answers to these must come from industry.

## Answering the questions

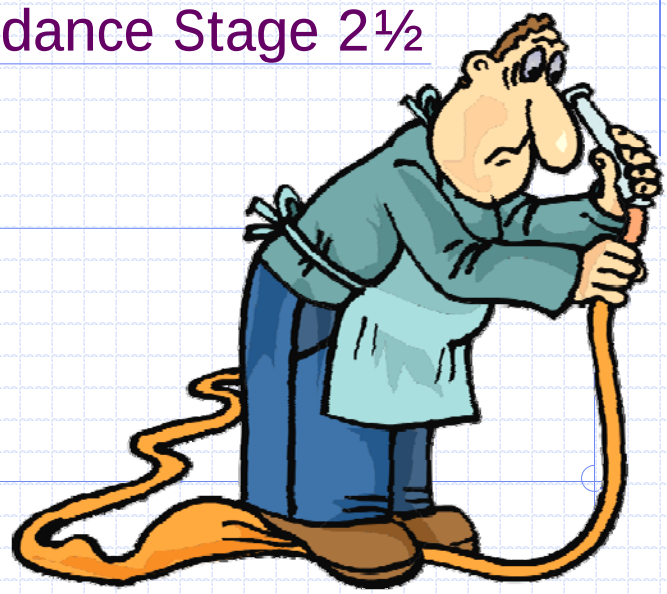
1. It's up the firm to make these critical decisions. FDA won't help.
2. The expectations will vary based upon risk based considerations:
   - The amount of information available from development to support the process.
   - The robustness of the process.
   - The availability of measurable in-process parameters linked to performance.
   - The firm's experience with similar processes.
   - The firm's overall risk tolerance.

## Some Basic Suggestions

- It should be obvious that the better defined the process the more reproducible the result.
- Basically forget 'statistically significant' as it relates to the number of batches. Very few products lend themselves to this. The statistical minimum is at least 15 batches and generally higher.
- Considering the elements on the last slide a single answer is likely not going to be appropriate in all instances.

# Stage 3
# Continued Process Verification
# (Validation Maintenance)

## PV Guidance Stage 2½



## There's a Stage 2½?!

- Stage 2½ - extensive sampling and testing of every batch as in Stage 2 with release on an individual basis (real-time comparison to prior results). When variability is understood and a routine sampling plan established this changes to ----->
- Stage 3 - sampling on a lower level of intensity with release on an individual basis (real-time comparison to prior results).

## FDA Stage 2½ Recommendation

- "We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level."

## Supportive CGMP Activities

## Stage 3 – Validation Maintenance

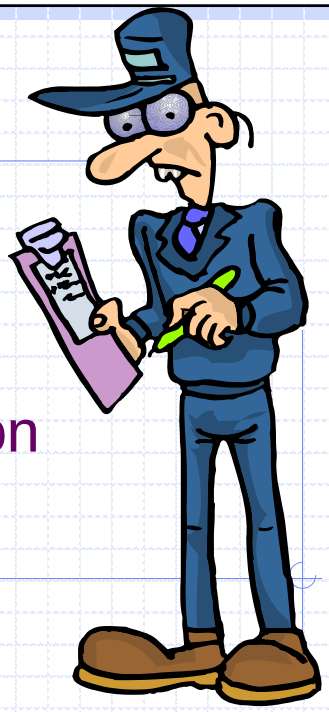
- This is the longest stage, it supports the continued acceptance of the process & its products for routine administration to patients. This has always emphasized change control.
- Added to that is an expectation for essentially 'real time' evaluation of a process against prior performance for near-immediate detection of process drift or unexpected change.

## CGMP & Maintenance of Validation

| | |
|---|---|
| Preventive maintenance | 211.67 (b) |
| Software security | 211.68 (b) |
| SOP's | 211.100 |
| Change control program | 211.100 |
| Calibration program | 211.68 |
| Regular QA reviews | 211.180 (e) |
| Equipment logs | 211.182 |

21 CFR 211 applies throughout manufacturing & packaging processes

## Stage 3 Real Time Process Verification



## Retrospective Vs Real-Time

- Establishing documented evidence that a process does what it purports to do based upon a periodic review and analysis of historical data.
- Was never well accepted by regulators
  - The results are essentially known before the data is gathered
- Confirming the acceptability of production materials using data collected and evaluated as it is developed.
- The essence of Stage 3 in the PV Guidance.
  - The results are evaluated in real-time against prior performance.

## Real-Time Process Verification

- The application of SPC control chart practices to product and/or process data in conjunction with lot release.
- It entails the review of individual lot results against the historical data derived from the same process.
- The goal is to provide a means for near immediate identification of potentially adverse variations in the product / process.

## Statistical Process Control

- On the surface this appears to have a lot in common with Stage 3 verification.
- The primary difference is that in SPC, the operator is empowered to make process adjustments on the shop floor.
- We can have that in certain areas and improve performance, but comparison to prior lots is something broader and should be performed by the Quality unit.
- We are also constrained by NDA / ANDA filings, sometimes requiring FDA approval.

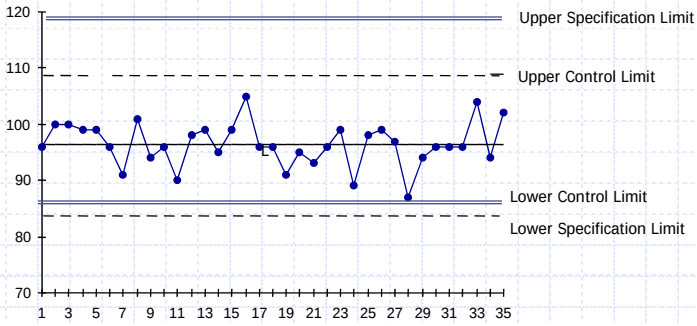
## Don't be Misled by the Compendia

- It contains an amount of XXX equivalent to NLT 95.0% and NMT 110.0% of the label.
- Acceptance criteria: 0.80–1.20
- NMT 1.0%
- NMT 20 ppm
- Acceptance criteria: 98.5%–101.5%

- These are typical pharmacopieal limits. That the last significant figure in these limits is always a '0' or a '5' suggests they have never been based on actual performance.

# Specification Limits/Control Limits

- Specification limits
  - Are set by the filed / pharmacopeial limits.
  - Describe what you *want* a process to achieve.
- Control limits
  - Are calculated ***from the historical data.***
  - Describe what the process is capable of achieving




# Limit Related Concerns

- Processes should be reasonably centered within the release specifications.
- Process variability must fall within the release limits.
  - If not the process is not capable and needs further improvement.
  - Setting internal control limits arbitrarily within release specifications and ignoring the process variability can make things difficult.
- The correct approach is to minimize process variability, and set internal control and specification limits accordingly afterwards.

## Stage 3 - Implementation

- The practices previously described should be in place for all products.
- If the product isn't capable, redevelopment or discontinuance are the only options.
- The rest of Stage 3 relies on existing practices mandated under 21 CFR 211.
- SPC type analysis of data in near real time is perhaps the best approach to maintain product quality & fulfill the guidance expectations. Pharma really isn't using SPC much at all.

## Concluding Thoughts

## Overall Perspective - 1

- The major themes aren't new at all.
- It outlines a solid approach to design / development / maintenance of reliable processes for making quality products.
- It mandates significant changes to the way in which industry develops, initially validates and maintains validated product/processes. The new guidance ups the ante substantially especially in the early stages of development.

## Overall Perspective - 2

- This guidance favors larger companies because they can afford extensive & expensive experimentation at early stages! Smaller firms will struggle with it largely because of resource limitations.
- CRO / Client / CMO interaction and transparency between them has to be taken to a new level.
- Low volume products (1-2 batches/year) are going to give everyone fits.

## FDA vs EMA Guidance - 1

- The differences in the guidance documents are not significant. Properly developed processes / products should meet the expectations of both EMA & FDA.
- The EMA uses the term 'continuous process verification' instead of PAT.
- The core expectations of both EMA & FDA with respect to process validation overall are nearly identical and likely to be more closely aligned in the future.

## FDA vs EMA Guidance - 2

- EMA tends to be more apprehensive with respect to novelty and identifies specific products / processes where additional concerns are present.
- There is substantially less mention in the EMA guidance with respect to the use of statistics.

## What wrong with the guidance?

- Substantial clarification is needed to either reconcile or exempt the guidance from applicability in non-formulation / synthesis situations.
- Sterilization development works to some extent, but the DOE & statistical elements are problematic in process confirmation.
- Aseptic processing must be force fit into conformance. It has huge statistical constraints, plus the variability of human behavior doesn't fit.
- The other non-product systems subject to validation can also be difficult to reconcile with the guidance.

## The 10,000 Foot View

| Activity | Approach |
|---|---|
| Utilities | Design very different, operational use with SPC trending possible |
| Environments | Design very different, operational use with SPC trending possible |
| Computerized | Life cycle use is the only similarity, statistics don't apply, really not applicable at all |
| Clean / Prep | Development is similar, but ongoing controls are weak, parameter linkage to performance is weak |
| Inspection | Design very different, operational controls are largely absent |
| Manual | Not a good fit anywhere regardless of process |
| Sterilization | Development OK, but similarity ends there |
| Aseptic | Few, if any, useable links from controlled variables to results |

## What else is wrong?

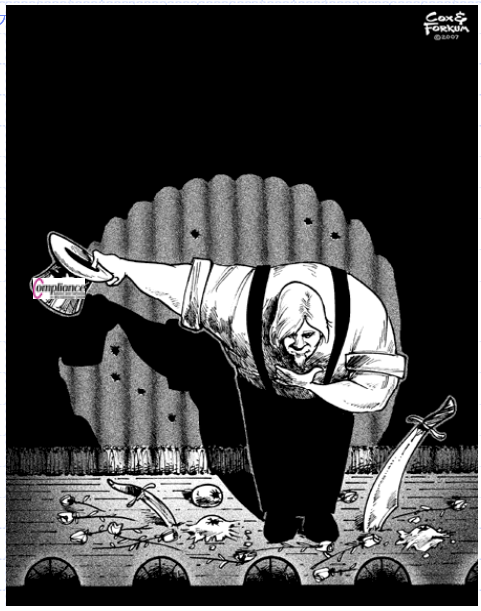
- Applying statistics to the number of validation batches is time consuming & expensive.
- An extensive effort is needed to develop a common understanding of expectations between FDA/EMA & industry (as well as within FDA/EMA & industry). It took 20+ years for common approaches to develop from the prior guidance of 1987.
- The critical questions must be answered by the industry and that's not being done efficiently or in an open enough manner.
- There's too many open questions and not enough broadly useable answers.

## Conclusion

- Implementing the guidance isn't difficult, we merely have to address the concerns in the right order and with the understanding that practiced in this manner we might realize some economic benefits from greater process reliability.

And think backwards at times as well!!

# Thanks for Your Attention!




Questions?

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