QPHARMA

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# New FDA Guidance:
# *Process Validation*

*A QPharma Training Topic*

*Presented by*

**Jeff Boatman, CQA**
Quality System Subject Matter Expert

## BACKGROUND: *GPOPV*

*General Principles of Process Validation*, FDA's seminal validation guidance, is being replaced.

- Core validation guidance for FDA since 1987
- Multiple FDA documents (GPOSV, GIHPWS, etc.) build on *GPOPV*
- Technically still current within FDA; long since superceded by more modern industry standards like GAMP5 and the ISPE V-Model
- GPOPV has only two phases, equipment and process
  - "Equipment" phase encompasses IQ and OQ (equipment is installed and operating correctly)
  - "Process" phase (includes PQ and "Product Performance Qualification").
- No Design Qualification
- No specific planning requirements
- No specific process development requirements
- No ongoing PV monitoring requirements

## BACKGROUND: CDRH

In 1996, the *Quality System Regulation* (21 CFR 820.70 and 820.75) introduced process validation as a regulatory mandate (i.e., not "optional" or "implied" by some vague implication such as 21 CFR 211.68).

- Directly applies to Medical Device companies
  - Indirectly applies to most other Life Science firms under 21 CFR 820.1(b)
- CDRH expectations far beyond *GPOPV*
  - Manufacturing process is part of product, so process development must be documented under design controls (21 CFR 820.30(d))
  - 21 CFR 820.30(g) requires separate product design (clinical) validation, essentially obsoleting concept of "PPQ"
  - Heavy emphasis on risk assessment (21 CFR 820.30(g))
  - Mandatory use of sound statistical methods (21 CFR 820.250)
  - Software supporting production must be validated (21 CFR 820.70(i))
  - PQ is the *START* of validation, not the end! (21 CFR 820.70(a)(2))

## BACKGROUND: CDRH (continued)

On June 15, 2006, CDRH released CPG 7382.845 *Inspections of Medical Device Manufacturers*

- Formally recognizes GHTF S3/99-10 *Process Validation*
  - and placed *GPOPV* "in limbo"
  - Not listed in CDRH's "Official Consensus Standards" List
- Phase-in target completion June 15, 2010

## BACKGROUND: CDER

On November 18, 2008, CDER (and CBER, CVM, and ORA…but *not* CDRH) released the draft *Process Validation: General Principles and Practices* for public comment.

- Explicitly obsoletes *GPOPV*
- Based on ICH Q8 (Pharmaceutical Development) and Q10 (Pharmaceutical Quality Systems)
- Part of ongoing modernization efforts under *21st Century Initiative*
- Minor technical differences from S3/99-10 but essentially the same with some additional GAMP design requirements
- CDER very clear that *PV-GPP* may technically be a "guidance" but they fully intend to enforce it with 483s and Warning Letters
  - Author Grace McNally told ISPE that Part 211 and existing practice makes it legally enforceable
  - If all else fails, CDER could always reference 21 CFR 820.1(b) to force compliance

## BACKGROUND: *PV-GPP* status

FDA received a *flood* of public comments on the new guidance, including over 200 comments from ISPE (and ten comments from QPharma)

- Massive confusion among experienced ISPE engineers
- Comment period was extended two months
- Target implementation was October or November 2009
- CDER insists that core requirements *will* be in final guidance
  - Will almost certainly have additional clarification
  - May get "toned down" or "phased in," *but*…
  - …*seems unlikely* that drug firms will continue to be subject to *less strict requirements* than device manufacturers for risk management, statistical controls, and ongoing monitoring

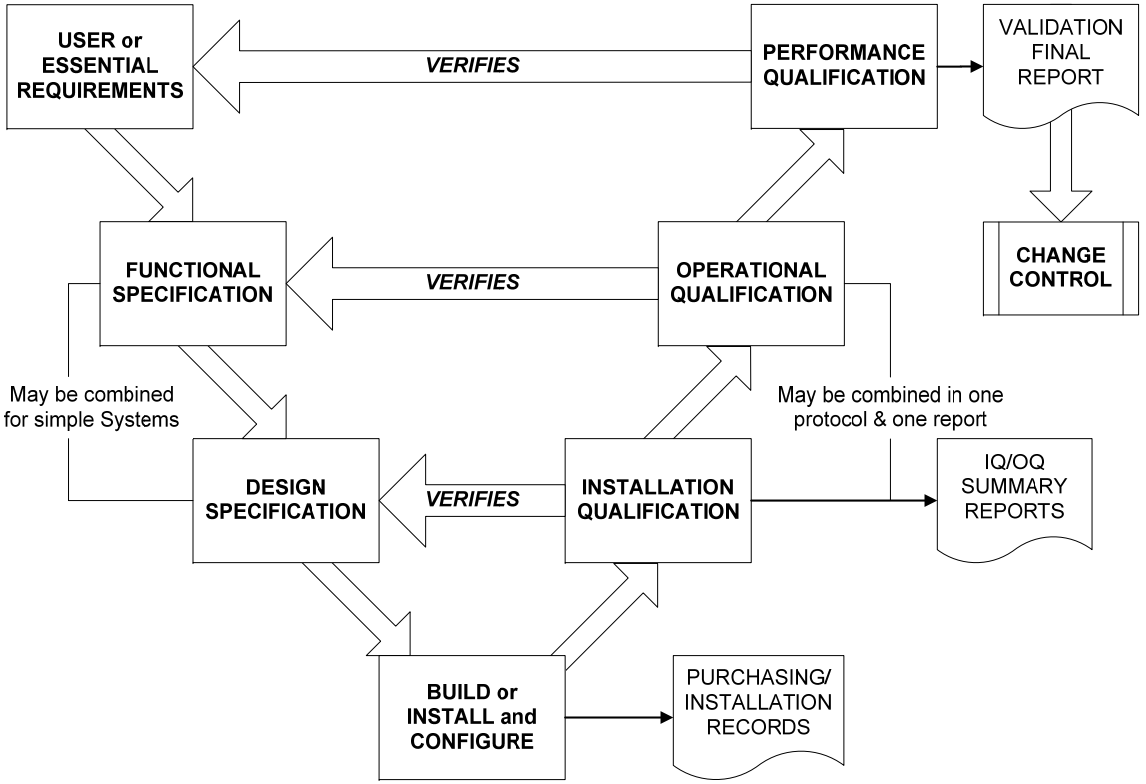
# VALIDATION 101

Validation means demonstration, by provision of objective evidence, that [*insert product or process*] consistently meets its predetermined requirements.

- Whenever a firm makes a *regulated claim* of compliance, that claim must be backed up by reliable evidence
- Doesn't matter what is claimed, so long as it is required by law or regulation
  - Efficacy of drug
  - Output of computer system
  - Safety of medical device
  - Usefulness of laboratory oven
  - Effectiveness of sterilizer
  - Ability of manufacturing process to consistently produce acceptable product

# VALIDATION 101 (continued)

The current *minimum* validation expectation for U.S. drug manufacturers is described in the ISPE "V-model":



## *Process Validation: General Principles and Practices*

The new draft describes process validation as an activity that coincides with the *entire product lifecycle*, with three "Stages":

- Stage 1: Process Design
  - Document the process during its development
  - Conduct *and document* engineering studies to identify and control sources of variability
  - Establish control limits that translate into product characteristics
  - Establish baseline variability data to be used as statistical basis
- Stage 2: Process Qualification
  - Similar to current V-model
  - IQ and OQ not stated (subject of many comments)
  - Increased vigilance during PQ (and, if Guidance remains unchanged, for some period afterwards)
  - Mandatory justification of statistical methods *including number of runs*
- Stage 3: Ongoing Process Verification
  - Control charting and statistical trending
  - Used as trigger for prospective correction and revalidation
  - Use in and relationship to APR (21 CFR 211.180) not stated

## *PV-GPP* Stage 1: Process Design

- Validation Project Plans now required…and *early*
  - Top management involvement
  - Defined and integrated validation teams
  - Mirrors medical device requirements in 21 CFR 820.30(b)
- Process Development under GDPs *regardless of GMPs*
  - Scientific rationale documented
  - Risk assessments mandatory (*but which methods?)*
  - Mirrors CDRH *Quality System Manual*: “Design Controls”
  - Design of Experiments expected to identify critical parameters
  - Critical parameters expected to become basis of batch records (mirrors 21 CFR 820.30(d)). *Implies that batch records must someday be traceable?*
  - Use of modeling (computer, FEA, mathematical) must be supported by documented applicability
  - Use of PAT recommended (another aspect of the *21st Century Initiative*)

# *PV-GPP* Stage 2: Process Qualification

- Facilities validation *mandatory* and *antecedent*
  - Requires careful planning
  - No more “outside scope”
  - Mentions “commissioning” but does not define or set expectations
  - Design Qualification still not mentioned (commissioning and DQ are often seen as European processes)
  - Directly in line with ISPE Baseline standard
- Equipment works over defined target range
  - Requires *really* careful planning (or expect to re-do a LOT of OQs)
  - Operational Qualification includes “intervention” (*meaning what?)*
  - Operating range must be held for as long as actual production use
    - *Even if validation defined in accepted industry standards?*
    - You may need to start scheduling OQs as carefully as PQs!
- One VMP, many PVPs…your choice – *but must address*
  - Changes to equipment and facilities
  - *Overall* acceptance criteria *including consistency between lines/machines*
    - Absolutely critical in setting up ongoing monitoring in Stage 3
    - Validation reports must address the acceptance criteria in the Plans

## *PV-GPP* Stage 2: Process Qualification (continued)

- Very little about OQ – expect more detail in final Guidance
- "PQ" confusingly used to mean both *Process* & *Performance* Qualification!
- Performance Qualification performed by *actual end users* following *actual procedures*
  - Not validation engineers using mock documents
  - SOPs approved or special controls in-place over drafts
  - Reflects ISPE Baseline standard
- Performance Qualification is subject to *increased vigilance*
  - Higher sampling rates (e.g. AQL Levels or sample sizes)
  - Sampling rates and acceptance criteria based on engineering studies
  - Necessary because…
- Performance Qualification is to be run at *nominal settings*
  - Experience with similar processes can be cited to limit PQ coverage
  - PQ does *not* challenge boundary conditions
  - Grace McNally's argument: PQ is making live product and boundary conditions should have been challenged in OQ; so no benefit and possible risk to challenging PQ
  - *Major* change in philosophy from *GPOPV*!

## *PV-GPP*: Performance Qualification Protocol

- Define controls, conditions, parameters, limits, raw materials
- What data will be collected and what it will be used for
- Each processing step must have a specific pass/fail instruction
  - No more “Push button and verify everything works”
- Specific instructions for amending protocols
  - May be in a validation SOP or VMP
- Describe sampling plans and their rationale
  - Sampling plans to be *more aggressive* than expected in normal production
- Describe inter- and intra-batch acceptance criteria
  - Must define permissible process “noise” and show process meets it
  - Without PQ baseline, future trending cannot distinguish between inherent “noise” and genuine process drifts
- Describe handling of non-conformances and deviations
  - If data can be excluded (outliers), Plan or Protocol must explain in advance
- What about IQ and OQ?

## *PV-GPP*: Performance Qualification Protocol (continued)

- Describe analytical methods and which ones must be validated
  - Methods used to validate Phase 1 clinicals need not be validated
    - Follows recent CDER guidance on clinical trials *but*
    - Unfortunately guidance does not align itself with clinical phases
  - In any event, lab equipment must include "scientific rational why methods are sound and sufficiently specific, sensitive, and accurate" and lab equipment must be "demonstrated to operate properly"
    - *So how is that different than "validated"?*
- State *how many batches needed and why*
  - Three batches no longer automatically acceptable (sorry).
  - Grace McNally explained: "Three is the minimum number, but number of runs has to be derived statistically" (not empirically)
  - *Still some old guidance documents that say three batches*
  - Hopefully FDA will clarify this in final Guidance
- Must be approved *prior to use*
  - Might seem like *common sense* but…

## *PV-GPP*: Reports

- Summary Report must draw *clear conclusion* as to whether or not process is fit and approved for use
- Any limitations e.g. products, parameters
- Can product produced during PQ be released
- Report must describe corrective plan if system failed
- Justification for any ongoing production use pending successful validation (not stated, but common examples include the following)
  - Processes for some products were successful
  - Work orders issued defining tighter limits on equipment operation
  - Inspection orders issued defining tighter acceptance limits or 100% inspection

## *PV-GPP* Stage 3: Ongoing Process Verification

Periodic review of process output to catch failures *before* they happen will be expected to be ongoing for the life of the product.

- While statistical trending of manufacturing may be new to some in the drug field, the medical device industry has been doing this for years
- Ongoing review to identify process drift
  - Method not explicitly stated, but common methods are
    - Control charting
    - CpK charting
- Continued use of "increased vigilance" after PQ until process history established
  - *Strongly* suggests CpK as monitoring method
  - Subject of *multiple* comments from industry!
- In any event, based on process information gathered during engineering studies, PQ, and subject to ongoing refinement
  - Already implied by Part 211 "Annual Product Review" and "narrow historical limits" language but never explicitly defined in old Guidance
  - Already required by 21 CFR 820.70(a)(2)

## *PV-GPP* Stage 3: Ongoing Process Verification (continued)

- Process Validation reviewed by *statistician* or engineer *trained in statistics*
  - While statistical trending may be new to some in the drug field, the medical device industry has been doing this for years.
- Periodic review of trending and maintenance data as revalidation trigger
  - SOP, MVP, etc.
  - *Implied* by 21 CFR 211.180(e)
  - *Required* by 21 CFR 820.75(c)
  - *Does this need to be included in CMC?*
- Procedures describe adjustment of Preventive Maintenance and Calibration procedures in response to process issues found
  - Already required for Medical Devices under 21 CFR 820.100

## *PV-GPP*: Required Documentation

- Process maps from Pilot and Commercial scale
  - Process and product flow, control points, monitoring and inspection points, inputs, and outputs
  - Included with planning documents
  - "Preserved for future use" (e.g. *as part of validation package*)
  - *Will CDER expect these to be part of CMC?*
- Process development plans and documentation
  - *Will FDA someday expect this documentation for legacy processes?*

# *PV*-GPP: Concurrent Release

## *"In theory,"* product can be shipped prior to PQ…

- Idea first appeared in *Quality Systems for Pharmaceutical Manufacturers*
- CDER followed up with CPG:
  - Must employ PAT
  - Must follow *QSFPM* (part of *21st Century Initiative*)
  - Must have successful validation *and* inspection record
- Product must be determined to be "medically necessary" (by whom? CDER? DO?)
- Must have "special systems" for early alert of field problems
  - Implies something beyond complaints and pharmacovigilence, but what?
- Bottom line: FDA expects exemption to be used rarely.
  - *If ever!*

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Thank you!

# Questions

and

# Critique