22 January 2009

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

**SUBMISSION OF COMMENTS, DOCKET NO. FDA-2008-D-0559**

Dear Sir or Madam:

ISPE is pleased to provide comments on FDA's "Draft Guidance for Industry on Process Validation: General Principles and Practices," the availability of which was announced in the November 18, 2008, *Federal Register* [Docket No. FDA–2008–D–0559].

**General Comments**

The document should contain a Glossary defining terms unique to the guidance or important to the understanding of it. Additional definition of terms is needed to add clarity to the guidance (i.e. "suitable for intended use", Process Qualification, Performance Qualification and Process Verification). This will also identify the distinction between deliverables for verification aspects related to facility and equipment versus "product."

The document should incorporate or reference the concepts and principles contained in ASTM E 2500-07 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* pursuant to the Food and Drug Administration Modernization Act of 1997 (P.L. 105-115), which amends section 514 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360d(c)). E 2500-07 is an international consensus standard "applicable to all elements of pharmaceutical and biopharmaceutical manufacturing systems including: facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems that have the potential to affect product quality and patient safety." As such, the concepts and principles of E 2500-07 should be incorporated into the Draft Guidance wherever feasible and appropriate to minimize confusion and foster harmonization.

**Specific Comments**

Please see the accompanying table. Line numbers therein refer to those of the Draft Guidance.

Yours sincerely,

Robert P. Best
President/CEO, ISPE

**ISPE Regulatory Comment Form**
**Proposed Regulation/Guidance Document:** **FDA, Draft Guidance for Industry, Process Validation: General Principles and Practices, November 2008**

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 1. | Section I | | Add to this section:<br><br>This guideline is only applicable for new products and new production processes. There is no need to restart validation activities for established marketed API, drug product and the utilities and equipment used for these products. | The guidance should be applicable only for new manufacturing process. For established marketed API and drug products there is no need to start new validation activities as result of this guidance. The process verification as requested in stage 3 is achieved by product quality review and production reports. |
| 2. | Line 37 and footnote | • Finished products and active pharmaceutical ingredients (API or drug substance)[3] | Clarify the relevance for APIs:<br><br>Either delete APIs from the scope of this guidance and refer specifically to ICH Q7A Section 12.4 for process validation guidance of APIs, or<br><br>Refer to Q7a as an additional source for general principles with details in this guidance.<br><br>The current wording of the footnote refers to the entire section 12 of Q7a which includes very prescriptive guidance on equipment, facility and utility qualification (12.3). This appears to be in direct contrast with the approach taken for all other facility types in Stage 2 a (lines 330-368). | The scope of the guidance with respect to APIs is not clear. In the introduction it is stated that APIs are within the scope of this document. Footnote 3 refers specifically to the entire section XII ICH Q7a, which "describes in detail the principles to be followed in validating API processes." Does this mean that Q7a gives the details of the expected process whereas this guidance describes only general principles for the validation of API processes?<br><br>There is an incongruity between recommending following a prescriptive qualification approach for API manufacturers and a less prescriptive one for all others. Industry and good engineering practice is well developed in regard to guidance for these activities which precede PQ. |
| 3. | Lines 52-54 | ...exclude the validation of automated process control systems ... | Requires explanation since automated systems are discussed at lines 196 – 198. | |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 4. | Lines 84 – 92 | – | Add a fourth bullet, or otherwise incorporate the idea that, “Product, process, equipment and facility design provide for adequate control of risks to the patient.” | One could argue that this is already covered by the word “safety” in line 85 and “quality attributes” in line 91, but since so much of the focus of recent guidance documents is related to risk management, it might be good to mention here. |
| 5. | Lines 90-91 | ...finished product meets all design characteristics and quality attributes... | Delete “design characteristics and” | The term “design characteristics” is superfluous. The product has to meet all quality attributes and not more. |
| 6. | Lines 93-95 | For purposes of this guidance, process validation is defined 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. | For purposes of this guidance, process validation is defined as the collection and evaluation of data, from the process design stage throughout production and commercial distribution, which establishes scientific evidence that a process is capable of consistently delivering quality products. | In order to truly reflect the product lifecycle (as specified in line 96), the collection and evaluation of data from product in commercial distribution should be included to capture product quality attributes, e.g., stability, breakage, and container-closure integrity, that might be affected in the distribution channels.<br><br>Adding the term “commercial distribution” to the definition is consistent with the expressed intent of the paragraph beginning at line 539 in the Continued Process Verification section. |
| 7. | Line 95 | ...quality products. | The term “quality products” should be defined. A suggested definition is “products fit for their intended use, meeting pre-determined specifications and quality attributes.” | Clarification |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 8. | Lines 111 – 118 | Before commercial distribution… | Move the last sentence, lines 116 – 118 and integrate into the thought conveyed by the sentence beginning at line 133. In other words, demonstrating a consistent commercial scale should not be required prior to distribution. | A high degree of assurance obtained from a variety of sources as described by lines 114 – 116 is a reasonable expectation. Demonstrating manufacturing consistency at the commercial scale should be an expectation within the first 15 – 30 batches manufactured at this scale, but not before distribution.<br><br>Lines 116 to 118 must therefore be also taken as "Before commercial distribution"… should have data that demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products… It is not commercially feasible to have statistically significant data that provide this demonstration – that would require a number of batches to be manufactured prior to distribution. |
| 9. | Line 132 | Focusing on qualification efforts without understanding the manufacturing process … | Focusing on process or manufacturing system qualification efforts without understanding the manufacturing process … | Clarification |
| 10. | Lines 160-161 | Product quality in the context of process validation means that product performance is consistent from batch-to-batch and unit-to-unit. | Product quality in the context of process validation means that product performance is characterized by homogeneity of the batch and batch-to-batch consistency. | Please clarify whether "unit" refers to "dosage unit" or to "production unit." |
| 11. | Lines 184 – 185 | This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability. | This requirement, in part, establishes the need for manufacturers to analyze process performance, make necessary adjustments to in-process parameters and control strategy, with the objective of controlling batch-to-batch variability. | Clarification |
| 12. | Lines 214-216, and footnote 8. | We recommend an integrated[8] team approach to process validation that includes expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. | Expand footnote 8 to also reference ICH Q9, Quality Risk Management, which recommends a multi-discipline team when analyzing risk to the patient. | Clarification |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 13. | Line 235 | ...critical quality attributes. | The term “critical quality attributes” should be defined. A suggested definition is “physical, chemical, biological or microbiological properties or characteristics that must be controlled (directly or indirectly) to ensure product quality.” | Clarification.<br><br>Note: The suggested definition is derived from ICH Q8R. |
| 14. | Lines 285 - 286 | Documentation should reflect the basis for decisions made about the process. | There should be some paragraph about “legacy” processes validation. | When transferring products from one site to another this information is often not available. |
| 15. | Line 326 and elsewhere. | Performance Qualification | Replace with Process Verification | The term “Performance Qualification (PQ)” has been defined by ISPE, GAMP, incorporated into the V-model and accepted by industry to mean performance of equipment, acting singly or in concert to meet a user requirement. For example, autoclave sterilization is a form of performance qualification to demonstrate the ability to sterilize. PQ also relates to sampling of water, steam, gas, and related systems, it can cover media fills, environmental monitoring, cleaning validation, as well as the operation of equipment together such as on a packaging line.<br><br>A substitute phrase to be used here could be “process performance qualification,” or “process verification.” Process verification probably comes closest in meaning to that described in the text. |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 16. | Line 330 | Qualification of Utilities and Equipment | Verification of Utilities and Equipment | The term Qualification associates the guide to a number of old practices for IQ/OQ/PQ etc. that does not support the new science- and risk based concept of QbD.<br><br>Although these "Q's" are not mentioned – which is good – the guide should clarify the difference between these old practices and the new.<br><br>It would also make the guidance consistent in wording with ASTM E2500-07 that has a similar aim of assuring that utilities, facilities and equipment are fit for their intended use. |
| 17. | Lines 334-336 | Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as *qualification*. | Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as *verification*. | This comment refers to a number of subsequent sections.<br><br>Furthermore it will ensure consistency with the wording in line 345 and 349 where the activities are called Verifying ("Verifying that utility systems and equipment are built and installed in…" and "Verifying that the utility system and equipment operate in…").<br><br>Consistency with ASTM E 2500-07. |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 18. | Lines 341- 367 | Qualification of utilities and equipment generally includes the following activities:<br>• Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific use.<br>• Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).<br>• Verifying that the utility system and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production.<br>Operating ranges should be shown capable of being held as long as would be necessary during routine production. | Qualification of utilities and equipment generally includes the following activities:<br>1. Identification of the significant aspects of the design, which are necessary to control the manufacturing process to assure the finished product will meet its quality attributes.<br>2. Identification of conditions that pose a high risk of process failure, and the significant aspects of the design, which may serve to control or reduce these risks.<br>3. Structured design incorporating design review, change management, and other good engineering practices to ensure the design meets the product and process requirements derived from process understanding and the process control strategy. This includes selection of materials of construction, operating principles, and performance characteristics, suitable for the intended use.<br>4. Use of commissioning and other appropriate steps to verify the utility systems and manufacturing equipment are installed and can operate to meet these signifcant aspects of the design, necessary to control the process and risks to process failure. Verification should include appropriate physical inspections, calibration of process measuring and control devices, functional testing, and performance challenges as expected during routine production. | These lines contain some very prescriptive and detailed instructions for what is essentially an engineering check-out. More importantly, the details in these lines are “old school qualification” content – they focus on design specifications rather than process requirements and controlling risk. The requirements listed in lines 357 through 367 are again prescriptive in terms of the documentation content (vs. the general guidance found at lines 588 and beyond), and extend well beyond what is required by 21 CFR 211.22(c). |
| 19. | Lines 358-360 | The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. | The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of verification activities. | Clarification: qualification and verification. |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 20. | Lines 360-367 | The plan should identify (1) the studies or tests to use, (2) the criteria appropriate to assess outcomes, (3) the timing of qualification activities, (4) responsibilities, and (5) the procedures for documenting and approving the qualification. It should also include the firm's requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan. The quality control unit must review and approve the qualification plan and report (21 CFR 211.22). | Suggest rewording to clarify that this is not as detailed as the IQ/OQ/PQ of the old industry practices. | The wording should be changed to clarify that this can be a high-level plan, not necessarily a detailed test execution plan like the validation protocols and test sheets of the past practices.<br><br>Emphasis here should also indicate alignment with ICH Q8R lifecycle principle that "*It is important to recognize that quality cannot be tested into products;*" |
| 21. | Lines 379-380 | The decision to begin commercial distribution should be supported by data from commercial batches. | Suggest rewording to clarify or correct for actual meaning. | It is unclear how data accumulated prior to a decision to distribute commercially can be obtained from commercial batches. It appears that the statement is contradictory as-is. |
| 22. | Lines 391 - 392 | In addition, we strongly recommend firms employ objective measures (e.g., statistical metrics), wherever feasible and meaningful to achieve adequate assurance. | It is generally considered acceptable that three consecutive batches or runs within the finally agreed parameters, would constitute a initial validation of the process, although we strongly recommend firms employ objective measures (e.g., statistical metrics), wherever feasible and meaningful to achieve adequate assurance. | The common practice of validating 3 consecutive batches could be arbitrarily rejected. |
| 23. | Lines 396-398 | This greater scrutiny accompanied by a higher level of sampling should continue through the process verification stage, as appropriate. | This greater scrutiny accompanied by a higher level of sampling should continue through the initial process validation stage (stage 2), as appropriate. | Clarification |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 24. | Lines 428-430 | The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. | The number of samples should provide adequate and scientifically based evidence of process and product uniformity, including statistical significance as appropriate. | Clarification |
| 25. | Lines 495-565 | | Add to this section:<br><br>For manufacturing processes produced infrequently and in small batch numbers it is not applicable to use statistical process control techniques for the process verification, instead of this, tools like production quality reviews or production reports are sufficient. | Stage 3 requirements, especially use of statistical methods, is not applicable for processes that are infrequently and in small batch numbers executed, e.g., one to three single batches a year. For such processes, statistical methods and procedures can not be used to evaluate process stability and process capability. |
| 26. | Line 502 | ... detection of process *drift*. | The term "*drift*" should be defined. A suggested definition is "a slow nonrandom change with time in the measured output of a process *when the input and process parameters are held constant*." Note: The italicized phrase in the proposed definition is optional. | Clarification |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 27. | Lines 533 - 537 | We recommend continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly. | Process variability should be periodically assessed. If significant variation is detected, we recommend increase the monitoring and/or sampling at the level established during the process qualification stage (or higher) until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level.<br><br>The level of effort, formality and documentation of the monitoring and/or sampling should be commensurate with the level of process knowledge. | Clarification |
| 28. | Line 574 | FDA expects that concurrent release will be used rarely. | FDA expects that concurrent release will be used rarely for initial validation. | The rare use of concurrent release should be specified for initial validation only. For the validation after minor changes or as revalidation if the annual review shows not enough statistical data for an evaluation, the concurrent validation is a wide spread tool. |
| 29. | Lines 598-601 | The degree and type of documentation required by CGMP is greatest during stage 2, process qualification, and stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see 21 CFR 211.22 and 211.100). | Suggest rewording to clarify that this is not as detailed as the IQ/OQ/PQ of the old industry practices. | The wording should be changed to clarify that these approvals can be on plans and reports that outline activities and acceptance criteria, not necessarily a detailed test execution plan like the validation protocols and test sheets of the past.<br><br>The focus for the documentation produced and of the quality unit's approval should be on documenting the significant product and process requirements identified using risk management principles; approving the appropriate acceptance criteria required to demonstrate compliance; approving the ability of the process and systems to consistently meet these requirements through the final report and monitoring the ongoing performance of the process to verify the achievement of consistent quality attributes. |

| No. | LINE NUMBER | CURRENT WORDING | PROPOSED CHANGE | RATIONALE |
|---|---|---|---|---|
| 30. | Lines 605-613 | CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record (21 CFR 211.186) and supporting procedures) are key outputs of stage 1, process design. We recommend that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision making about their comparability. | Add a statement as the last paragraph of section VI such as: A key output of phase II is the verification of utilities and equipment. The documentation supporting this type of verification should be commensurate with the requirements of use and risk management priority. | Add guidance on the distinction between “CGMP documents for commercial production” and documentation for equipment-based verification. This will augment the statements made in 358-360. |
| 31. | Line 610 | ...(e.g., processing aids)... | The term “processing aids” should be defined or examples should be provided. | Clarification |