BIOTECHNOLOGY INDUSTRY ORGANIZATION

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January 21, 2009

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-D-0559, Draft Guidance for Industry on Process Validation: General Principles and Practices; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Process Validation: General Principles and Practices.* BIO welcomes this guidance from the Agency and agrees with most of the high level concepts put forth in the document. BIO member companies concur that validation is a lifetime cycle activity, and that the general approach of 3-lot validation does not truly ensure that a process operates under a state of control. This guideline will facilitate the full realization and benefits from the International Conference on Harmonisation's (ICH) Q8, Q9, and Q10 guidances, describing process validation for products wherein a Quality by Design approach has been applied, especially over the early part of the life cycle of the product.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. BIO is pleased to offer the following comments in support of the guidance.

I. TERMINOLOGY AND NOMENCLATURE SHOULD BE APPLIED CONSISTENTLY AND ALIGNED WITH ICH DOCUMENTS:

BIO believes that the guidance would be enhanced through more consistent application of nomenclature and alignment with previously defined terminology. We strongly recommend that FDA use terms as defined in previously published ICH documents. BIO requests that where new terms are introduced (such as validation stages 1, 2, and 3), that the guidance please provide clear definitions.

For example, the document uses "Qualification" and "Validation" interchangeably (example: line 132). BIO recommends using the following terminology consistent with the definitions in ICHQ7.

- *Qualification*: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.
- *Validation*: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

In addition, it would be helpful to provide definition and/or clarification on the following:

- *Process Design* (what is included, early phases, experiments)
- *Product Development Activities*
- *Impurity*
- Relationship between *Process Characterization* and *Process Monitoring* when making major process changes
- Applicability of *Retrospective Validation* (especially with regard to statement on Line 85 and in relationship to legacy products).
- *Design Space* and relationship to *Process Validation* principles and practice

BIO also believes that the guidance document could be improved and potential confusion avoided through better incorporation of the principles of critical quality attributes and critical process parameters. In many places throughout the document, better alignment of terminology with terminology in ICH Q 8, 9 and 10 would greatly improve and better harmonize this guidance with existing ICH quality guidance. A few examples are listed below:

- Line 91: change "design characteristics" which is not defined in ICH to "Each step of a manufacturing process is controlled to assure that the finished product meets its critical quality attributes and performance characteristics as defined in the target product profile."
- Line 114: change "those attributes relating to identity, strength, quality, purity and potency" to "its critical quality attributes"
- Line 267: change "multifactorial interactions" to "multivariate interactions"
- Line 289: change "strategy for control" to "product control strategy"
- Line 291: change "Establishing a Strategy for Process Control" to Establishing a Product Control Strategy"

- Line 510-511: change “verify the critical quality attributes are being controlled throughout the process” to “the product control strategy consistently ensures that critical quality attributes and product performance characteristics are achieved.”

II. CLARIFICATION IS NEEDED REGARDING STATISTICAL METHODS

BIO also requests additional clarity regarding references to statistical sampling in the draft guidance (e.g., lines 427- 432). We note that not all samples taken can be statistically justified, such as ID testing. BIO recommends adding “where appropriate”, and suggests the manufacturer should justify the sampling plan. For example, “The number of samples should be adequate to provide sufficient statistical confidence, where appropriate, of quality both within a batch and between batches.” Indeed, it would be unusual to have sufficient data to apply meaningful statistical evaluation of data during drug development, prior to manufacture of approximately 30 lots at commercial scale. BIO also requests that FDA allow for flexibility in the use of statistical methodology consistent with process and product knowledge, stage of development and type of product. For example, orphan drugs will generally have few lots available at all stages of development and commercialization and thus the data available for rigorous statistical analysis will be limited.

III. CGMPS FOR SMALL SCALE STUDIES:

BIO believes that small scale impurity removal studies in support of the commercial scale manufacture should be conducted consistent with appropriate application of Current Good Manufacturing Practice (CGMP) concepts. These CGMP concepts include good documentation practices and should be supported by sound science to ensure validity and traceability of the data. We agree that viral removal and inactivation studies should be conducted under appropriate phase specific CGMPs due to the potential impact to patient safety. Laboratory evaluation of these samples should be conducted under CGMP conditions when they are used to support a license application.

IV. EXPECTATIONS SHOULD BE ALIGNED BOTH AMONG AND BETWEEN REVIEW AND INSPECTORATE STAFF:

We agree that determining minimal requirements for commercialization is best done on a case-by-case basis taking into account the process, product type, patient population and knowledge base. We are concerned, however, about consistency of application of this approach both within and between the review and inspectorate staff. We ask FDA to ensure alignment within the inspectorate and review groups and between the review and inspectorate groups.

V. CLARIFACTION IS REQUESTED FOR LEGACY PRODUCTS AND PRODUCTS NOT DEVELOPED UNDER FULL QBD:

As noted previously, this guidance will be beneficial in describing process validation for products wherein a Quality by Design approach has been applied, especially over the early part of the life cycle of the product. However, for existing legacy products and/or products currently developed with less than full QbD approaches, the guideline, as written, may be difficult to apply. In order to bridge the different expectations between this new guidance and existing practice for products that are not developed under full QbD, a risk-based approach may need to be applied when changes that generally require validation are made to legacy product processes. Also, we request that FDA confirm that a non-QbD approach to product development remains an alternative, and thus validation for these non-QbD products should employ a risk-based approach relative to the concepts in the new guidance.

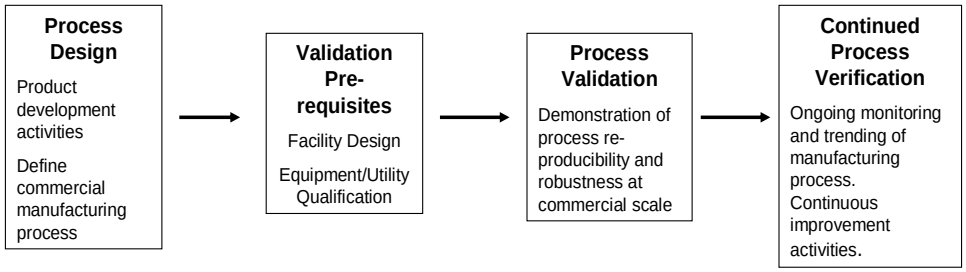
VI. TOPICS FOR FUTURE ICH DISCUSSIONS:

To maximize the impact of this effort to update the approach to validation on a global scale, it might be reasonable to consider this as a topic for future ICH efforts. In lieu of an ICH document on this topic, FDA might maximize the impact of this effort to update the approach to validation on a global scale, by including reference to other consensus guidance documents. This includes:

- General – ASTM E2537-08, Continuous Quality Verification Standard
- Line 315 – ASTM E2474-06, Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology
- General or Line 336 – ASTM 2500

SPECIFIC COMMENTS

BIO is please to offer the following specific comments in support of the guidance. *The cells highlighted in gray indicate the areas of primary concern for BIO member companies.*

SECTION	ISSUE	PROPOSED CHANGE
I. BACKGROUND		
Lines 93-106:	It will generate unnecessary confusion to change currently accepted terminology that is widely used within the industry. It is already understood that Process Design is a prerequisite for validation and that post-validation monitoring is required to detect potential process drifts. We propose that the entire process (process design through monitoring) be termed the Validation Lifecycle. The term Process Qualification, used here to describe stage 2 activities, is later described as being composed of equipment qualification and Performance Qualification, here referring to demonstration of commercial manufacturing capability. The term Performance Qualification is already commonly used as the final step in equipment qualification and is supported by ICH Q7 and EU Annex 15 definitions which support this meaning.	It is therefore recommended that the term Process Validation continue to be used to describe demonstration of reproducibility at commercial scale and that Performance Qualification continues to describe the final phase of equipment qualification. A schematic diagram would be helpful to convey the intended scope of this document (eg. as below) **Validation Lifecycle** 
Line 102:	We recommend replacing "Process Qualification" with "Process Validation". Examples include line 102, lines 132-133, and lines 287-288.	Line 102: "Stage 2 – Process Validation" Line 132-133: "Focusing on validation efforts without understand the manufacturing process may not lead to adequate assurance of quality."

		Line 287-288: "This information is useful during the process validation and continued process verification stages,…"
Line 103:	While the existing requirement for three consecutive successful process validation runs has statistical significance limitations, it has at least harmonized industry (and FDA inspectors) to some degree on process validation approaches. This document provides no guidance on the minimum expectation for the number of runs during process qualification, in essence allowing the manufacturers to determine the amount of data necessary to qualify a process. While this does encourage flexibility and scientific thought, it also may prompt disharmony amongst manufacturers and within industry, as well as be cause for debate during inspections, as inspectors may have varying opinions on the validity of the approach, due to the subjective nature of this document. Further, it may open the door for disagreements between review staff and inspection staff at FDA. This same comment may apply to the continuous process verification section which requires "sufficient data".	Please provide guidance or a discussion regarding minimum expectations for the number of runs during process qualification.
Lines 99-106:	We would like to have better distinction between Stages described in the draft guidance. What needs to be completed when? Especially applies to Stage 1.	Please clarify expectations for stage 1 as described in the draft guidance. Please clarify information that is to be included in the filing vs. data that are expected to be available upon inspection.

	Also, the scope of what is to be included in filing vs. data available upon inspection is unclear.	
Line 105:	We recommend replacing "Continued Process Verification" with "Continued Process Monitoring".	Substitute "Continued Process Monitoring" for "Continued Process Verification".
Lines 111-129:	Sources of variation such as complex cell growth medium components are difficult to assess and understand without the knowledge gained from use of many raw material lots over many years of production.	Change line 111 from 'Before any batch from the process is commercially distributed for use by consumers, a manufacturer. . .' to 'During process qualification and continued process monitoring…'
Lines 116-118:	We recommend substituting "high degree of assurance" for "demonstrate", because the totality of the information and data including those from laboratory- and pilot- scale studies can only provide a high degree of assurance that the commercial manufacturing process is capable of consistently producing acceptable quality products under commercial manufacturing conditions. In addition, this language is consistent with language used elsewhere in the guidance (lines 112, 130-131)	We recommend changing the text to read: Information and data should provide a high degree of assurance that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions, including those conditions that pose a high risk of process failure.
Line 130:	We recommend replacing "judge" with "evaluate", since this document will be used where English is not the native language and there could be misunderstanding when translated.	"Each manufacturer should evaluate whether it has gained sufficient understanding…"

II. STATUATORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION		
Lines 118, and 259-262:	Clarification on expectation for testing to failure is needed.	Please revise to state: "Laboratory or pilot-scale models, designed to be representative of the commercial process, can be used to estimate variability. While it is expected that an understanding of process risks and variability is gained, it is not a regulatory expectation that the process be tested until it fails".
IV. RECOMMENDATIONS – A. General Considerations for Process Validation		
Line 208:	'good project management and good archiving' is unclear.	Please be more specific on what is meant and/or provide examples or comparisons for clarity
Line 208:	We recommend including a reference to knowledge management as an enabler to the pharmaceutical quality system as outlined in ICH Q10.	Include a reference to knowledge management as an enabler to the pharmaceutical quality system as outlined in ICH Q10.
Lines 208 – 212:	We recommend revising the verbiage in this section of the document for clarification.	"In all stages of the product lifecycle, practices should ensure uniform collection and assessment of information about the process, and enhance the accessibility of such information later in the product lifecycle."
Line 209:	Meaning of the term: "process validation program"	With respect to a validation program we seek more clarity on process validation versus product validation. For example, can a family approach be used? See comments on line 413.
Lines 214 – 217:	We recommend revising the verbiage in this section of the document for clarification.	"We recommend an integrated team approach to process validation that includes expertise from a variety of disciplines to allow for a more comprehensive review."
Line 215:	'industrial pharmacy' doesn't seem to fit in this list	Please eliminate 'industrial pharmacy' or clarify why it is in the list
Lines 215-216:	We recommend add flexibility.	Correct to read: "…variety of disciplines, including for example process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance, depending upon the nature of the particular operation being validated."

Lines 216 – 217:	We recommend revising the verbiage in this section of the document for clarification.	"Project plans are essential elements for success."
Lines 217:	Senior management, while ultimately responsible for appropriate execution, is generally not involved in the detail of project plans for validation. Senior management is involved with overall management plan for process validation, not necessarily detailed planning.	Please revise to state: "Project plans and oversight or reviews at routine intervals by appropriate management are essential elements for success." Please also reference ICH Q10.
Line 245:	As previously noted, please clarify that only appropriate aspects of CGMP need to be in place for small scale studies (e.g. of virus removal). For example, it would be important to have quality involvement and oversight and CGMP documentation practices. However, other aspects of CGMP controls, as used during commercial production, may not be required.	Suggest revise to read "…should be performed under CGMP conditions *as appropriate* ….." When the text refers to impurity clearance studies, it should be clarified whether this is referring only to biological and biotechnology products or to all API manufacturing.
Lines 245-248, and Lines 601-602:	Per ICH Q5A Guideline, "Viral clearance studies are useful for contributing to the assurance that acceptable level of safety in the final product is achieved but do not by themselves establish safety". These studies are executed with model or relevant viruses to assess overall process capability with respect to virus clearance. Data from these studies serve as a surrogate baseline for estimating the ability of the process to clear other viruses having similar physico-chemical characteristics. Given	Remove mention of impurity clearance for reason stated. If not removed, please clarify whether this applies to biotech products only or to all APIs. Revise paragraph beginning line 245 to read: "There are exceptions, however. Given that viral clearance studies are a key component used to help establish drug safety, the sponsor quality unit should be involved to ensure that the bench scale operations were performed as expected and that the results reported for the study are supported by the raw data". Revise sentence line 601 to read: "The sponsor quality unit should be involved with viral clearance studies to ensure that the bench scale operations were performed as expected and that the results reported for the study are supported by the raw data".

	that these data are essentially an approximation of the clearance capability for all virus types, conducting the actual processing portion of the studies under cGMP conditions would add no additional assurance of product safety. Additionally, it is not clear how full GMP expectations could even be applied to bench scale operations. Adherence to cGXP (either GMP or GLP) is warranted for the viral assay and testing procedures used to determine the clearance values for a given unit operation, as this provides an appropriate level of assurance that the assays are reproducible, accurate and sensitive enough to estimate process capability. Bench scale impurity clearance studies are not executed to provide drug safety assurance, but rather used to establish process clearance capability that is verified during validation at commercial scale.	
IV. RECOMMENDATIONS – B. Specific Stages and Activities of Process Validation		
Stage 1 – Process Design		
Lines 230-289:	When does Stage 1 start and how formal is it meant to be? Does it include production of material for Phase 1 clinical studies? Is this consistent with recent Phase 1 guidance on more flexible approaches to GMP at this stage?	Please clarify. Also see the specific comment on line 237.

Lines 237-238:	It is not general practice to conduct most process design experiments under CGMP conditions. The draft guidance suggests that mid and late stage experiments should be conducted under these conditions.	Please revise to state: "Process design experiments should be conducted and documented in a manner that allows the accumulated data and resulting knowledge to be easily accessible." Please clarify what is meant by "early".
Lines 228-289:	The terms "process design experiments" and "product development activities" are not defined and it's not clear that they represent different activities.	Please clearly define what is meant by the two activities.
Lines 245-248:	Please clarify the expected involvement of the Quality unit in validation studies that are performed at a reduced scale. Does FDA mean to apply additional involvement beyond what is currently expected in review and approval of protocols and reports?	Please revise to state: "...we strongly recommend firms employ objective measures and acceptance criteria to achieve adequate assurance that the process operates in a state of control." We are concerned with the phrase "cGMP conditions" since Q7 allows more latitude. However, we agree that the quality unit should be involved with these studies.
Lines 264 – 273:	Design of Experiment (DOE) can be useful during later stages as well, possibly more commonly when anticipating commercial scale – see line 284-289 for discretion. This is part of the product lifecycle.	This section that describes DOE, multifactorial interactions, and establishment of ranges for incoming components and parameters should make the connection to the concept of Design Space as described in ICH Q8.
Line 284:	We recommend revising this line for clarification.	Correct to read: "It is essential that activities and studies resulting in product and process understanding be…"
Line 287:	We recommend revising the verbiage in this section of the document for clarification.	"It is essential that activities and studies resulting in product understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as critical. "

Line 291:	We propose revising the title of this subsection of the document to use the term "control strategy" as defined by ICH Q10, as creation of additional terminology may be confusing. It would also be beneficial if this section on Establishing a Strategy for Process Control could be more firmly linked to the concept of Control Strategy described in ICH Q9 (R1). The same terminology, Control Strategy, should be used in both documents. Use of common terminology would be consistent with the intent expressed in the introduction to align with the ICH documents.	"b. Establishing a Control Strategy"
Stage 2 – Process Qualification		
Line 321:	As expressed above for lines 93-106, the term Process Qualification should be replaced with Process Validation.	The term Process Qualification should be replaced with Process Validation. The sections on facility design and equipment and utility qualification could be moved to a new section, or it can be clarified in this section that these activities are pre-requisites to Process Validation.
Lines 333 – 336:	By reversing the order of these two sentences and introducing the term qualification first, it reinforces the concept that design and commissioning should be completed prior to qualification. Otherwise, the term commissioning takes the place of qualification.	Please revise to state: "Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for intended use and perform properly is referred to in this guidance as qualification. It is essential that activities performed to assure proper facility design and commissioning precede PQ."

Lines 336:	As ASTM E 2007 uses the term "verification", to better align with regulations, and we recommend aligning the terminology.	"Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly are referred to in this guidance as *verification*."
Lines 354-355:	Qualification of equipment should demonstrate operation representative of manufacturing conditions and use.	Please delete lines 354-355 or move to section b. Performance Qualification, perhaps following the sentence ending on Line 375.
Lines 354 – 355:	This line states "*Operating ranges should be shown capable of being held as long as would be necessary during routine production*". Strict application of this principle would require unnecessary time and resources and is not science-based. For example, demonstration of control and reliability should be based on potential for variability in a given application. As a result, we recommend revising the verbiage in this section of the document.	"Operating ranges should be shown capable of being maintained as would be representative of routine production."
Lines 357 – 367:	We recommend removing the verbiage in this section of the document and refer to ICH Q10 in terms of the change management element.	We propose removing the verbiage in this section of the document and refer to ICH Q10 in terms of the change management element.
Line 366:	We recommend clarifying this phrase.	Suggest rephrasing "quality control unit" to "quality unit", as "quality unit" is the term used throughout the rest of the document. In addition, the Quality Control Department is not necessarily involved with all equipment validation activities; however, the Quality Assurance Department always is.
Line 369:	The validation activities occurring under "Performance Qualification" in this guidance document conflict with the definition of performance qualification	Change title of section 2b to "Approach to Process Qualification"

	in ICH Q7 which addresses verification that the equipment and ancillary systems, connected together, can perform effectively and reproducibly based on the approved process method and specifications. These activities are described as qualification under section 2a of the guidance document which creates confusion with existing guidance on validation activities. This confusion could be addressed by changing the title of 2b to Approach to Process Qualification.	
Line 371:	Definition of PQ: process qualification vs. performance qualification	Semantic issue: What does the abbreviation "PQ" stand for? As it reads, PQ is an element of PQ; this nomenclature may be confusing. In addition the term "performance qualification" in this document seems to conflict with definitions of PQ and PV in ICH Q7. See also comments for lines 569-579.
Line 379:	We recommend clarifying the verbiage in this section, as data from commercial batches cannot be accumulated prior to a decision to distribute commercially.	"The decision to begin commercial distribution should be supported by data from commercial validation batches."
Line 385, 389 and 403:	The term 'commercial' in commercial batches should really be revised to reflect the scale of the process, not the intended use of the material. Commercial batches imply to some that the material was produced for commercial distribution, i.e., commerce. Data from production or commercial-scale batches should be acceptable for establishing that the batches were manufactured appropriately.	Please revise from "commercial batches" to "commercial-scale batches" or "production/production-scale batches" in Lines 385 and 403.

Lines 389 – 392:	We recommend revising the verbiage in this section, as this sentence as written could lead to confusion around what is 'credible' and what is 'sufficiently similar'.	"Previous experience with similar products and processes can also be considered."
Line 391:	The draft guidance encourages use of "statistical metrics" whenever feasible during process qualification (PQ). In general, a meaningful statistical analysis cannot be performed with the small number of lots that will be available at the initiation of commercial distribution. Statistical analysis becomes meaningful during routine manufacture when data from at least 30 full scale lots have been produced. Also, various references are made to the use of statistical methods and analysis, (statistical confidence (429), statistical methods (437), confidence levels (430), variability estimates (535) and similar terms). It is not clear what degree of statistical scrutiny is expected (e.g. calculation of Cpk, assurance of 95% confidence levels, etc)	Please revise to state: "…we strongly recommend firms employ objective measures and acceptance criteria to achieve adequate assurance that the process operates in a state of control."
Line 394:	We recommend clarifying that only in "some" cases, PQ will require additional testing and scrutiny.	Correct to read: "In some cases, PQ will have a higher level of sampling, additional testing, and greater..."
Lines 394-398:	Intensity of sampling depends upon the circumstances and best time to apply resources.	We disagree with this statement as sufficient evidence should be obtained during the process qualification stage to demonstrate a controlled process; therefore, the intensified sampling plan during the process qualification stage should be allowed to be reduced to a more normal (routine) evaluation testing scheme during the process verification stage. To require the intensified sampling and testing scheme after process

		qualification places a huge burden on the quality control laboratories. Under what conditions should there be greater scrutiny? Can a substantial amount of development data to mitigate higher sampling levels? Please clarify.
Line 396:	While we can appreciate the value of some additional testing (in addition to routine sampling and testing) for a few batches post validation, if we have developed the process by QbD principles and have a thorough process understanding prior to validation, full validation level testing of output from all unit operations (after validation) seems unnecessary. Suggest that additional testing of end product CQAs satisfies the desire to provide additional patient protection immediately after initial process validation. If unexpected results or trends are identified, additional testing of earlier unit operations could be performed as part of the investigation.	While we can appreciate the value of some additional testing (in addition to routine sampling and testing) for a few batches post validation, if we have developed the process by QbD principles and have a thorough process understanding prior to validation, full validation level testing of output from all unit operations (after validation) seems unnecessary. We suggest that additional testing of end product CQAs satisfies the desire to provide additional patient protection immediately after initial process validation. If unexpected results or trends are identified, additional testing of earlier unit operations could be performed as part of the investigation.
Line 397:	While an enhanced sampling plan is an integral aspect of performance qualification, it is essential that the testing applied be meaningful with regard to quality attributes.	Please revise to state: "The level of monitoring and testing, and the selection of tests relevant to critical quality attributes, should be sufficient to confirm uniform product quality throughout the batch during processing."
Lines 408-409:	We recommend clarifying this language.	Recommend revising sentence to read: "The accuracy of the measurement tool should be verified during the process design stage and the process qualification stage"
Line 413:	The family approach, which may be defined as "a process validation approach that allows for a reduced	We request additional discussion and guidance regarding the family approach.

	number of validation studies when using equipment of equivalent design, manufacture and operational functionality" is a commonly utilized approach throughout the industry, but it is not discussed in this document.	
Line 413:	As in the comment to line 369 use of the term "Performance Qualification" conflicts with the definition in ICH Q7.	2c. Protocol for Process Qualification
Lines 416-417:	It would be helpful to revise the sentence to make the connection between Stage 1 and Stage 2	Recommend revising sentence to read: "Based upon knowledge base developed during earlier stages and/or small-scale studies, we recommend that the protocol discuss:"
Line 425:	We recommend revising the verbiage in this section of the document for clarification.	"Tests to be performed (in-process, release, characterization) and acceptance criteria for each critical processing step."
Lines 428 – 429:	These lines state the number of PQ samples should "…provide sufficient statistical confidence of quality both within a batch and between batches". The requirements contained in this section could become burdensome on manufacturers. As an example, in liquid solution manufacturing validation, one could interpret this statement to imply it be expected to pull 30-50 samples per batch to demonstrate homogeneity, and then a statistical treatment of the 90-150 (assuming a 3-lot validation) samples across all validation lots. We suggest that this section be reassessed. During initial process qualification, adequate data may not be available to	We recommend revising this section to state: "The sampling plan including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. Where appropriate, the number of samples should be adequate to provide sufficient confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage is typically more extensive than during routine production. Provide justification for the sampling scheme." FDA should clarify the degree of statistical scrutiny expected (e.g. calculation of Cpk, assurance of 95% confidence levels, etc)

	assess the inter- and intra-batch variability. The requirement should be changed to be a stage 3 requirement as part of monitoring and should require an assessment and justification of the specifications that will be monitored on a routine basis. The analysis of all testing specifications may not add value. As in the comments regarding statistical analysis in line 391, it would be rare to have sufficient sampling to demonstrate statistical confidence both within and among batches. There are various references to use of statistical methods and analysis, (statistical confidence (429), statistical methods (437), confidence levels (430), variability estimates (535) and similar terms). It is not clear what degree of statistical scrutiny is expected (e.g. calculation of Cpk, assurance of 95% confidence levels, etc)	
Line 463:	We recommend revising the verbiage in this section of the document.	Please revise to state: "Where the process operating ranges have been justified and previously documented, the PQ lots should be manufactured under normal conditions…"
Line 464:	The expectation that personnel who perform the PQ operations should "...personnel expected to routinely perform each step..." is unrealistic and excessive. Staff who participates in PQ activities should be trained, but there should be no requirement that they be the same staff who will participate in commercial manufacture.	Please revise to state: "The PQ lots should be manufactured under normal conditions by trained personnel."

Line 457:	We request clarification.	Please clarify whether "departure" is equivalent to "deviation"
Line 459 – 460:	Some protocol exceptions must or do happen in real time so pre-approval is not possible.	Please eliminate 'before implementation' from line 460.
Line 460:	We request clarification.	We recommend revising sentence to read: "…quality unit before final approval of the study and implementation of the process (§ 211.100)."
Line 469-470:	To align with similar statements in this guidance, it is suggested to replace "in a timely manner" to link closing process validation with the commercial distribution.	Please revise to state: "… should be prepared after the completion of the protocol and prior to commercial distribution of product."
Stage 3 – Continued Process Verification:		
Line 495:	The newly described "Stage 3" (starting at line 495) on ongoing monitoring needs further clarification as to intent. Annual reviews of quality data to assure ongoing control are specifically required by 21 CFR 211.180(e). Requirements specified in this guideline can be redundant with the Annual product review process.	It should be clarified how this section adds information and how process validation feeds into the Annual Product Review process as specified in 21 CFR 211 180(e).
Lines 513 – 515:	The focus here should be on the scientific approach and methodology needed for evaluating process capability rather than the qualifications of the person conducting the activities.	Please revise to state: "Sound scientific principles utilizing statistical methods and procedures be used in measuring and evaluating process capability."
Line 539:	Variation may not be detected by trending of defect complaints or adverse event reports.	Please change 'can' to 'sometimes may'.

V. CONCURRENT RELEASE OF PERFORMANCE QUALIFACTION BATCHES		
Lines 569-579:	Clarity on intended scope of PQ activities and definition of PQ	We request clarification of definition of PQ -- performance qualification or process qualification? Does the "prior to distribution" requirement apply to e.g. validation of SIP circuits which may be concurrent? The word "rarely" may not be appropriate. See also comments for line 371.
Lines 574 – 579:	This statement may be true for new products, but would not be applicable where confirmation runs are done to support a change to a well-understood existing product, or where the change is better demonstrated through stage 1 studies and stage 3 monitoring. An example would include material from a new vendor meeting the same specifications as the existing vendor, where it is difficult to obtain adequate quantities of different lots material to perform the stage 2 confirmation runs.	We propose revising this section to state: "FDA expects that concurrent release will be used where the development stage and on-going monitoring best represent the process, for processes used infrequently because of limited demand for the product (e.g., orphan drugs), processes with necessarily low production volume per batch (e.g., radiopharmaceuticals, including positron emission tomography drugs), and processes manufacturing *medically necessary* drugs to alleviate a short supply, which should be coordinated with the Agency."
Lines 584 – 586:	We recommend explaining the expectation all batches in a concurrent release program are place on stability.	Please revise to state: "Each batch on a concurrent release program should be considered for stability testing based upon the attributes of the batch and knowledge of the stability characteristics of the drug product."
Lines 592 – 596:	We recommend acknowledging the requirements in this section refer to knowledge management as discussed in ICH Q10.	Acknowledge the requirements in this section refer to knowledge management as discussed in ICH Q10.
VI. DOCUMENTATION		
Line 622:	(In Analytical Methodology) there should be a statement added about precision. Without acceptable precision, in-process test results are statistically meaningless.	Please revise to state: "…methods should be scientifically sound (e.g. specific, sensitive, accurate and have acceptable precision).

VII. ANALYTICAL METHODOLOGY		
Lines 626-627:	We request clarification.	Stage 2 and 3 are generally done with commercial lots. Was this meant to be Phase 2 and 3? Methods should validated by Stage 2/3 which can often be commercial lots with finalized process.
Line 626:	The final sentence addresses clinical supplies, but uses the term "stage 2 and 3 studies". The wording should be revised to "phase 2 and 3 studies", since stage 2 and stage 3 are earlier described as components of the validation lifecycle approach (lines 99-106) It is unclear from this sentence whether stage 2 and 3 refer to phase of process validation or phase of clinical trial. Reference to parts 210 and 211 are confusing in that this applies to API as well as drug product The final sentence addresses clinical supplies, but uses the term "stage 2 and 3 studies".	Please clarify use of the terms "stages 2 and 3" as described within this guidance and Phase 2 and 3 clinical development stages.
Lines 626 – 627:	We recommend revising the verbiage in this section to clarify when validated methods are required.	We suggest the following: "Analytical methods supporting studies having direct impact on product released to market or needed for performance qualification must follow appropriate cGMPs in parts 210 and 211."

CONCLUSION:

BIO appreciates this opportunity to comment on the *Draft Guidance for Industry on Process Validation: General Principles and Practices.* We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Director for Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)