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March 3, 2009

Division of Docket Management
Food and Drug Administration
5630 Fisher Lane, Room 1061
Rockville, MD 20852

Reference: *Guidance for Industry Process Validation: General Principles and Practices*; Federal Dockets Management System Docket FDA-2008-D-0559

Dear Sir/Madam,

The Parenteral Drug Association (PDA) is pleased to offer comments on the FDA Draft *Guidance for Industry Process Validation: General Principles and Practices.* PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in process validation and were reviewed and approved by PDA Advisory Boards and Committees. PDA appreciates the opportunity to offer comments on this Draft Guidance and wishes to thank FDA for the opportunity to do so.

PDA Response to the FDA Process Validation Guidance Revision

In order to develop representative comments on this comprehensive guidance, PDA solicited input from a broad range of its members and formed a working committee to review, organize and prepare our comments. We received over 400 comments, indicating strong interest in this long awaited document. We wish to stress that our membership and the committee feel that the guidance is a good document which will advance the new quality paradigm, consistent with the science and risk based approach FDA is advocating. As such, we have organized these comments into a spreadsheet which is available on PDA's web page (www.pda.org), as a service to our membership and as an adjunct to this summary document which addresses primarily recurring categories of comments. The categories are presented in order of priority of the subject, as interpreted by the PDA.

We welcome the sprit of the drafted guideline to implement the new paradigm of a science and risk based approach. The following are the six major

categories of comments received from PDA respondents for clarification. The category is used as a reference to the expanded list of comments (made available separately on the PDA web page).

Wording and Terminology

This category on the use and definition of specific terms and language had the most questions and comments. Collectively, these comments promote the value of including a document glossary, as well as the desire to use terminology which is consistent with ICH and other FDA regulatory guidance definitions in order to reduce potential misinterpretation. It is felt such updates could be achieved without altering the intent of the guidance.

Some examples include:

- the difference between 'design stage' vs. 'product development stage'
- 'continued process verification' vs. 'continuous quality verification'
- process qualification vs. performance qualification
- use of ICH Q9 terms (e.g. risk analysis, risk control)

PDA believes many of these comments are valid, because this document will be used as a guide by a diverse section of the industry with varied levels of experience with a varied range of terminology; including many international firms and sites. Clarity and consistency of language will help those companies interpret and meet with the expectations presented in the guidance.

Approach and Assurance for Commercial Distribution

There were several questions and comments on expectations for determining the level of assurance required to initiate commercial product manufacture and release batches for commercial distribution. Related to this issue was the concern that a limited number of developmental batches would not be sufficient to develop a statistically sound rationale for commercial product distribution. The guidance indicates extensive testing on early commercial batches to achieve statistically sound process controls might be required, yet offers no indication of expectation for what constitutes the acceptable level of assurance in order to reduce this level of testing. The guidance was interpreted not to allow risk assessment as a means to reduce the number of samples and level of monitoring on relatively low risk processes and steps.

PDA recommends FDA allows for and encourage the use of risk assessment to determine the level of testing and data required to achieve the acceptable level of assurance needed to release batches for commercial distribution, and ongoing evaluation. To satisfy the concerns of these respondents, the PDA suggests the concept of risk assessment described in Stages 1 and 2 should be applied in Stage 3 and throughout the process and product lifecycle.

Viral and Impurity Clearance

Our members expressed objections relative to the expectation of viral and impurity clearance studies performed at small scale under full CGMP conditions. Many of these comments cited inconsistencies with other guidance including ICH Q5A, ICH Q10, and European guideline CPMP/BWP/268/95. There were also requests for clarification on the implication that impurity studies included both biological and small molecule API impurities. Comments contended that these studies are typically performed at small scale laboratory levels under GLP conditions and should not require full CGMP conditions. Performing these studies under full CGMP procedures would be burdensome and fail to add benefit or value.

PDA recommends that the wording in the draft guidance suggesting that viral and impurity clearance studies be performed under CGMP conditions, even when performed at small scale, be removed. This requirement is out of scope in a general process validation guidance. In addition, it is overly prescriptive when compared with the rest of the guidance and inconsistent with current regulatory guidance.

Concurrent Release

Several concerns were raised on the recommendation for stability testing of all concurrently-released batches. PDA feels that a recommendation to conduct additional post-market surveillance of concurrently-released (CR) batches implies an apparently lower confidence threshold for the release of those batches. It should be clear to industry, and consumers that batches released under a CR program have the same level of product quality as batches released after a prospective validation program. Therefore, PDA suggests that the recommendations for enhanced *post*-market analysis be removed,

Scope and Legacy Systems

Scope – There were several questions and comments requesting clarification of and changes to the scope of the guidance. These included clarifying whether the guidance covered clinical product supplies, investigational medical products, blood products, in-vitro diagnostic products, and vaccine products. These also included questions related to whether processes such as cleaning, sterilization, sanitization, holding and distribution of commercial products were included in the scope of the guidance. While the committee felt that some of these questions were addressed in the guidance, it was notable that respondents experienced in the field of validation expressed concerns and required additional clarification. This reflects the potential for confusion regarding the scope of the guideline. PDA recommends that FDA reinforce that the Guidance is intended to be applied to direct commercial product manufacturing processes; for example synthesis and formulation.

Some comments registered concern over the mention of “single source” products and “production output and (product) supply problems” and asked if this indicated the agency expected qualification and validation of systems which do not affect product quality, but

otherwise do affect product availability. If this is the case, then it represents a significant departure from current industry practice. PDA believes that the references to assuring product supply should be removed or the guidance should clarify that it does not cover processes which do not affect product quality, but may affect product supply.

Legacy Processes and Systems - Clarification was sought regarding the application of this guidance to existing products and processes. The guidance did not appear to address the agency's expectation for these systems and processes; specifically to what extent these systems and processes should be validated with the new approach and to what extent systems previously validated would be "grandfathered". While PDA agrees that companies should utilize the approach presented in this version of the guidance to confirm that systems and processes continue to operate in a validated state, we recommend the guidance clearly indicate that full "revalidation" of existing systems and processes is neither expected nor required in the manner described in the draft revision.

Qualification, Documentation, Organization and Regulatory Impact

Qualification - There were several comments on clarification of equipment, utility, and facility qualification expectations and interaction; including expansion of facility and process design qualification/review and commissioning. Significant concerns were expressed regarding the expectation to demonstrate the capability of equipment to maintain operating ranges over anticipated production times, especially where extended processing times are encountered. Such qualification approaches should be risk and engineering based. In addition, there were comments expressing concern over inconsistencies in terminology for segments of facility qualification.

PDA believes current industry practices and developing techniques surrounding execution, documentation, and approval activities for commissioning and qualification are appropriate and further regulatory input is not needed.

Documentation and Organization- There were several comments requesting clarification of documentation expectations for all stages of process validation, in particular the clarification of qualification plans versus protocols. We also recommend removal of language which prescribes organizational dynamics and personnel activities such as having a variety of disciplines and "project plans" (lines 215-216) and trending production line operator's errors (lines 541-545).

PDA believes the guidance should not make recommendations related to how validation efforts should be named or how the execution team should be organized.

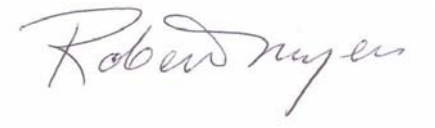
Regulatory Impact – There were several comments requesting clarification of regulatory submission, reporting impact, and inspection expectations related to process validation. While PDA understands these issues to be clearly excluded in the document scope, FDA may wish to update related submission guidelines where such discussions are provided.

Summary

The PDA and the committee are pleased to have had the opportunity to develop comments on this document and hope it assists FDA to finalize the guidance. As our large number of comments suggests intense interest in our membership and more than likely the general industry, we feel it will be invaluable for further public discussion in the form of a workshop or other means of shared learning.

PDA offers its further assistance to explain or provide additional information on the comments or to otherwise assist the FDA in this endeavor. When these have been conducted in the past, there is greater understanding and faster acceptance both by industry and the regulators of new guidance. If FDA wishes to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,



Robert B. Myers

President, PDA

CC: Robert Dana, PDA

Rich Levy, PDA

Version 8; 3-2-09

PDA VERBATIM MEMBER COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY: *Process Validation: General Principles and Practices*

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Key to Comment Categories:

A. **Wording and Terminology**
B. **Approach and Assurance for Commercial Distribution**
C. **Viral and Impurity Clearance**
D. **Concurrent Release**
E. **Legacy Systems and Scope**
F. **Qualifications, Documentation, and Regulatory Impact**

Category	Line No.	Current Text	Proposed Change	Rationale
A	Footnote 2		Add reference to ICH Q8(R1)-Annex	Document approved now by ICH
E	6-8	Guidance is silent on legacy products	Soft commentary about existing processes already designed and developed; Principles within this guidance may be considered but retrospective work is unnecessary.	There is room for review and analysis of existing data for legacy processes.
E	24	Clarify clinical vs. commercial manufacturing process that are validated. Two comments received on clarification of clinical supplies mfg.	Add commercial to: " …validating a ***commercial*** manufacturing process…"	
E	28	…qualification of the commercial manufacturing process, and maintenance of the process in a state…	Suggest replacing the word 'qualification' with 'validation'	Confusing as many of the international guidances restrict 'qualification' to systems, and 'validation' to processes

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Category	Line No.	Current Text	Proposed Change	Rationale
A	29-30	Modern manufacturing principles	Define what is meant by "modern" somewhere or use more accurate language – "manufacturing principles based on current best practices"	Need specific language that is meaningful and clearly understood
E	32	"drugs"	"drugs and vaccines"	Specifically include vaccines within scope if they are within scope or note after line 40 that they are not within scope
E	32	The following… within scope…		What about Blood Products
A	34	The different category words mentioned as the same category in the scope of this guidance. •Human Drugs (snip) •Finished Products …	Please clarify the definition of "Human Drugs" in this guideline.	For better understanding
E	36	Biological and biotechnology products	…products including in-vitro diagnostic biotechnology products	Confusion on application of guidance for in-vitro diagnostic biotechnology products.

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Category	Line No.	Current Text	Proposed Change	Rationale
E	line 37 and footnote 3		Clarify the relevance for APIs: a) Delete APIs from line 37 as being out of the scope of this guidance and refer to ICH Q7A Section 12 for process validation of APIs, or b) Refer to Q7A as a general principle description with details in this Guidance (or vice versa, depending on intent)	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 to ICH Q7A, which "describes in detail the principles to be followed in validating API processes. This implies that Q7a gives the details whereas this Guidance describes only general principles for the validation of API processes?
F	48		- add requirements appropriately -	It should be clearly stated which Process Validation stage has to be completed at the time of submission/filing and for the pre-approval inspection.

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Category	Line No.	Current Text	Proposed Change	Rationale
E	52-55	This guidance also does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. This guidance is relevant, however, to the validation of processes that include automated equipment in processing. Automated equipment in processing	Add…but does not rule out the use of this guidance….	Wording suggests that one cannot qualify hardware interfaces such as PLCs using this document
E	53		Need to add that guide does not specifically discuss validation of other systems such as equipment either since the details of validation of all these systems are outside the scope of this guide.	After parents, add "and other supporting systems (e.g. facilities, utilities, equipment)".

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Category	Line No.	Current Text	Proposed Change	Rationale
A	79	The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).	The CGMP regulations for pharmaceutical (drug) manufacturing require that drug products be produced to assure that they have the identity, strength, quality and purity they purport or are represented to possess.	Change to exact wording of CFR. (there is no specific mention of validation in that section – that is FDA interpretation of the text). Furthermore, these requirements only apply to drug product and not to API whereas the guide specifically says that it applies to API and drug product.
A	81		Please delete 'significantly'	Use of the word 'significantly' downplays importance of other aspects of a Quality System
A	85	Quality, safety and efficacy are designed or *built* into the product	Quality, safety and efficacy are designed into the product	Built is a loose term and doesn't add anything that designed doesn't cover – choose a new word or delete "built"
E	85		Address older processes in which design and build are not apparent	New paradigm is regulatory burden for existing processes, e.g. blood fractionation
A	85	Quality, safety, and efficacy are designed or built into the product	Quality, safety, and efficacy are designed and built into the product	One needs to have an adequate and approved design before proceeding into product build. This is an essential concept in Change Control

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Category	Line No.	Current Text	Proposed Change	Rationale
A	90	Controlled, but not necessarily "validated"	Controlled (but not necessarily validated)	
A	90	Each step…	Each "critical" step	Many process parameters are not critical and the level of control is somewhat less than critical process parameters
A	90-91	Each step of a manufacturing process is controlled….all design characteristics and quality attributes including specifications	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	Change in line with ICH Q8 definitions whereas "design characteristics" is not defined anywhere

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Category	Line No.	Current Text	Proposed Change	Rationale
A	Terminology (examples on line 93-106 and throughout the document)	Revised definition of PV & use of PQ term. Term control strategy is not used.	The steps may be represented as design, execution and monitoring of PV. The entire approach (process design through monitoring) could be termed the Validation Lifecycle. The control strategy concept should be incorporated/addressed in the guidance.	The terms are inconsistent with terms used in industry guidance (e.g. PQ in ISPE Engineering Baseline guide) and regulations and guidance from other regions (e.g. ICH Q7, EU GMP Guide Annex 15). 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. It is useful to reflect the current acceptance in the guidance.
F	93-109	Defines stages	Add a section or some commentary on documentation expectations	Document should minimally discuss a validation plan and expected documentation elements

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Category	Line No.	Current Text	Proposed Change	Rationale
A	93-95	Process validation is defined as….	Process validation is the provision of scientific evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined critical quality attributes and performance characteristics. Process validation is a lifecycle activity.	As written in the draft, the definition is not consistent with any currently understood concept of validation. Validation is a confirmatory action and is not part of development. It is well established that development must be completed prior to performing validation whereas the novel definition that FDA suggests is likely to confuse scientists in particular and make life harder for Quality professionals. Furthermore, there is no definition as to what constitutes a "quality product." The proposed change in wording is also consistent with the definition provided in line 410 of this guide as the goal of process validation
A	95	Quality Products	Meeting predetermined specifications	Current term is too vague – keep consistent with other FDA docs.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	99		Suggest to replace: 'Process controls' by 'control strategy' or state that 'Process controls is equal to control strategy if an QbD type process is uses'	Use wording according ICH Q8 & ICH Q8(R1)
A	99-100	Stage 1 – Process Design: The commercial process is defined….	Delete or move to a section called "activities required prior to Process Validation"	Definition of the commercial process is NOT part of validation. It is a pre-requisite to validation in exactly the same way as writing a cleaning SOP is a pre-requisite to performing cleaning validation. Including this as a first step in process validation is likely to confuse industry and result in process optimization being considered as validation – it has taken many years to establish that optimization should be completed before validation.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	102	Process Qualification	Process Verification	The next step is called "continued process verification" so logically I would think that the previous step would be process verification. Additionally, there is a sub-step of Process Qualification called Performance Qualification. This leads to two PQ abbreviations in the same document and same step. The "process verification" name change would eliminate this potential source of confusion and also put this document in agreement with other guidance such as ISPE Baseline Guide 5 (2008 draft revision)
A	102	Process Qualification	Process Confirmation	Agreement with the Compliance Policy Guide (7132.08- 2004)-

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Category	Line No.	Current Text	Proposed Change	Rationale
A	102	It is recommended to replace "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…"
A	102-103	Stage 2 – Process Qualification	Change to Stage 1 and have two stages as follows: Stage 1 – Initial Process Qualification: during this stage the process is demonstrated to be capable of repeatedly producing product meeting its Critical Quality Attributes and Performance Characteristics Stage 2 – Commercial Process Qualification: During this stage,	Initial qualification may not be on commercial batches, so that reference to commercial should be deleted. It is not the process design that is shown to be reproducible – it is the process itself. If FDA feels it is important to stress that correct design is a prerequisite for this an alternative wording might be: "during this stage the process is demonstrating as having been designed to be capable of repeatedly producing….."

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Category	Line No.	Current Text	Proposed Change	Rationale
A	105 (Stages)	Stage 3 – Continued Process Verification	Stage 3 – Ongoing Process Verification: Ongoing confirmation throughout the product lifecycle in commercial manufacturing that the process is consistent and remains in a state of control	Clarity: Better indicates a lifecycle activity
E	105 (Stage 3-legacy)	This draft guidance includes no descriptions on how to deal with legacies for Stage 3.	To minimize any unnecessary confusions or misunderstandings in practical situations, the guidance should include a clear statement on the scope of "Continued Process Verification".	Does this guidance expect a "Continued Process Verification" for all the currently approved products or only for new products of which validation activities follow this guidance from the first stage of their lifecycle?
A	105	"Continued Process Monitoring"	It is recommended to replace "Continued Process Verification" with "Continued Process Monitoring".	
A	105 (Stage 3)	There is no description about "Design Space" in this draft guidance. The relation between Continued Process Verification and Design Space is not clear.	Please clarify the relation between Design Space mentioned in ICH Q8 and Continued Process Verification. Is it acceptable to confirm that performance of process is within the range of Design Space with Continued Process Verification?	The relation between Design Space and Continued Process Verification should be clarified.

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Category	Line No.	Current Text	Proposed Change	Rationale
B	112; 130/131	"…a high degree of assurance in its manufacturing process…"	There needs to be a clear definition of what constitutes a 'high degree of assurance.'	In Stage 3, which occurs after commercialization, the guidance states at lines 525-527 that "a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed," so how could this happen after a 'high degree of confidence," how much information would be considered enough?
B	113	"objective information and data from laboratory-,pilot-, and/or commercial- scale studies"	Define more clearly what is intended by this phrase objective information and how that differs from data from lab, pilot, commercial	Objective information is loose phrase to be interpreted in many ways
A	114 and 157		Please include complete list of quality attributes – safety, identity, strength, quality, purity and potency	
B	114	The assurance should be obtained…	The assurance should be obtained from a scientific evaluation of data from…..	Clarity. Scientific evaluation requires objective information and is consistent with the principles of sound science advocated by FDA
E	114		Address older processes in which design and build are not apparent	Increase understanding of inexperienced companies

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Category	Line No.	Current Text	Proposed Change	Rationale
A	114	…meeting those attributes relating to identity, strength, quality, purity, and potency.	not consistent with footnote no 6 at the bottom of the page that says "to assure that the identity, strength, purity and quality.."	
A	114		Replace identity, strength, quality and potency with safety and efficacy	
A	114	…meeting those attributes relating to identity, strength, quality, purity, and potency.		is the term API quality attribute related to the API molecule(s) only, or does it include API formulation components? – please clarify
A	116-118 260-262		Please place a period after the phrase 'manufacturing conditions' and delete the remainder of the sentence, or provide examples of when this is permissible.	The guidance uses the term "conditions that pose a high risk of process failure". This implies that is permissible to operate manufacturing process under conditions which pose a high risk of process failure.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	116	Information and data should demonstrate 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 failure.	Data should demonstrate that manufacturing process is capable of consistently producing product meeting its Critical Quality Attributes and Performance Characteristics, under commercial manufacturing conditions, including those that pose a high risk of failure.	Delete "information" which is not a scientific term. Delete first use of "commercial" – redundant Change "acceptable quality products" which lacks any definition to recognized terminology.
B	118		Implies lots of testing to failure	Clarification (refer to line 259 below)
B	118	"including those conditions that pose a high risk of process failure".	Use the term "relatively high risk of failure"	Settings within the specifications will pose a relatively high risk of failure not an overall high risk
B	118	…including those conditions that pose a high risk of process failure.	…including those conditions at the allowable limits of the routine operating process.	Process validation is confirmation of the process, running at process failure does not confirm consistent operation as defined by the process. Stage I in defining the design space should already establish the limits

Category	Line No.	Current Text	Proposed Change	Rationale
B	116-118 118 (261)	…including those conditions that pose a high risk of process failure	Delete last clause and instead state "It is beneficial to develop understanding of conditions that pose a high risk of process failure." --- Clarify that EOF is not being validated --- Delete last phrase of 118.	With last clause "…including those conditions that pose a high risk of process failure", statement interpreted as meaning we should be demonstrating how to prepare product using high-risk conditions at commercial scale. --- We do not typically validate EOF , not even for a design space filing --- I interpret both sentences to say that commercial processes should be consistently capable even under conditions that have a high risk of failure.
B	118		Delete the phrase ", including those conditions that pose a high risk of process failure"	Confusing phrase that seems to imply that we should do testing to failure which is not feasible most of the time

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Category	Line No.	Current Text	Proposed Change	Rationale
B	118	…including those conditions that pose a high risk of process failure	End the sentence after manufacturing conditions. Delete including…high risk of process failure	Manufacturing processes should not be designed with a high risk of process failure. Manufacturing processes should be designed within conditions that result in acceptable product. Therefore, I would focus the validation efforts on commercial manufacturing conditions and not those conditions that would result in or be near the process failure point.
B	120	A successful validation program depends on information and knowledge from product and process development	A successful validation program depends on understanding and knowledge gained from product and process development	Clarity / consistency. Use of "information" is not scientific and does not place emphasis on product / process understanding which is critical to the success of the validation. Furthermore this is the terminology used in the following sentence.
F	120-129	Defines elements	Add a section or some commentary on documentation expectations	Document should minimally discuss a expected documentation elements

Category	Line No.	Current Text	Proposed Change	Rationale
A	121	This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process	Understanding and knowledge gained from development studies, together with Risk Assessment methodologies, forms the basis for establishing an appropriate Product Control Strategy for the manufacturing process.	
A	122	Manufacturers should:	Prior to initiating process validation manufacturers should: • understand the sources of process variability • be capable of detecting the presence and degree of variation both between and within batches • understand the impact of variability on the process and ultimately on Critical Quality Attributes • ensure that the process design is capable of controlling variables in a manner commensurate with the risk that they represent to process and product	These are all pre-validation activities that form the basis for verification and confirmation as part of the validation protocol. In order to avoid confusion it should be clarified that these points need to be established as part of the manufacturing instructions *prior* to initiation of validation

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Category	Line No.	Current Text	Proposed Change	Rationale
B	124-128		Add " this can be done via the use of RM tools or the appropriate statistical methods"	Industry needs to get a bit more specific guidance on how these can be accomplished
A	125		'variation' to be replaced by 'discrepancy'	Avoid misunderstanding with EU regulatory procedures
A	130		Consider replacing 'should' with 'needs to'	The use of the word 'should' implies that there may be circumstances in which the FDA would find it acceptable for a manufacturer NOT to gain full knowledge of its manufacturing process prior to commercial distribution of the process. This appears to be contradictory to the strategies outlined in the remainder of the document.
A	130		"Each manufacturer should evaluate whether it has gained sufficient understanding…"	It is recommended to replace "judge" with "evaluate", since this guidance will be used where English is not the native language and there could be misunderstanding when translated.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	130	Each manufacturer should judge…	Each manufacturer should judge whether it has gained sufficient understanding to allow it to embark on formal process qualification so as to provide a high degree of assurance that the process will always yield a product meeting its CQAs.	Clarity – emphasizing that the process validation cannot start until the development has reached a point that its data provide evidence of process understanding
A	132	Qualification efforts	Confirmatory efforts	
A	132		Suggest to add: '.. understanding the manufacturing process *and its risks* may lead to….'	Also if a specific event is not completely understood controlling the risk to patient can be sufficient (See ICH Q9 1st principle)
A	133	"after establishing and confirming"	"after validating"	More specific terms than establishing and confirming and the heart of this document. Otherwise define what is meant by establishing and confirming
A	133	Confirming the process	Confirming <u>reproducibility</u> of the process	We are concerned with reproducibility
A	134	…manufacturers must "maintain" the process	…manufacturers must "maintain and periodically confirm " the process	Defines expectation for some time driven confirmation of ongoing performance

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Category	Line No.	Current Text	Proposed Change	Rationale
A	134	…manufacturers must maintain the process…	…must maintain and periodically reconfirm and document as part of a requalification and validation program….	Periodically confirm and document is part of a preventive requalification and revalidation program.
A	135	…materials, equipment, production environment, personnel, and manufacturing procedures change.	Add the words, automation and software	These are also areas that can change independently during commercial manufacturing.
A	138	Statutory and Regulatory Requirements	Add references to ICH Q7	The section appears to reference only 21 CFR part 211 but the guidance applies to APIs as well
A	Section III (138-203)		It is recommended to remove this section, as a summary, referred to as an Annual Product Review, is already a requirement per regulation, and this section provides unnecessary commentary to the guidance.	
A	157		Potency not listed	Clarification
A	160	Product performance is consistent	Performance, within specifications,	If bad performance is consistent then that is OK?
A	161	Many products are single-source or involve complicated processes to manufacture	Many products have complex manufacturing processes.	Clarity Either define what “single-source” means or delete

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Category	Line No.	Current Text	Proposed Change	Rationale
E	161	.. .single-source…	Change to multi-source, as this appears what is meant (it is more complex than single-source)	Mentions single source products in the context of variability, which is confusing
A	161		Consider replacing the line with: 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 the word “unit” refers to “dosage unit” or to “production unit“.
E	161-162		Consider deleting the sentence.	The sentence ‘Many products are single-source or involve complicated processes to manufacture’ seems to be misplaced in this paragraph. It does not support the arguments or examples in the remainder to the paragraph, nor is it referred to later in the document.
B	161-2	Validation also offers assurance	Suggest modifying the sentence to specify the following: “Information, i.e., appropriate justification from formal risk assessment, and data should demonstrate . . .” (it is only implied that risk assessment is done)	This paragraph provides recommendations about “how assurance should be obtained” without reference to risk assessment

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Category	Line No.	Current Text	Proposed Change	Rationale
E	162-164		Should update guidance to reflect that consistent product quality as defined by critical quality characteristics should be the key focus of validation.	Seems to tie production output (yield) to patient health based on product supply. Production output may not always have this impact. Typically this would be a business (noncritical quality) concern.
B	162	Validation also offers assurance...	Validation provides assurance	Clarity
B	162-164	"Validation also offers assurance that a process is reasonably safeguarded from sources of variability affecting production output…"	There needs to be a definition of how much validation is supposed to get involved in production and supply issues	Is validation to consider capacity issues? How about contingency plans, such as when a hurricane hits Puerto Rico?
B	161-164	Many products are single-source or… affecting public health.	Remove these sentences.	Output and supply do not affect product quality.
B	164	Supply problems		This is not really a 'validation' issue
B	178	In-process …consistent with …final specifications...	Clarify	This could be a problem if they are referring to blend assay. (..in-process consistent with final specs...)
A	180-181	..in-process material should be controlled…	The sentence should be softened and imply that IPCs may be part of the overall control strategy (along with other considerations).	The IPC discussion is only part of the overall control strategy

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Category	Line No.	Current Text	Proposed Change	Rationale
A	181-185	"…derived from previous...need for manufacturers to analyze process performance and control batch-batch variability"	The reference to the regulations should be accompanied by an explanation that "the need for manufacturers to analyze process performance and control batch-to-batch variability" can be achieved by an evaluation of a combination of control criteria that may include but is not limited to results within design space boundaries, trending data and operating ranges within specification limits.	While we do not dispute the explicit expectations described in the regulation being quoted, additional clarity of its applicable intent is necessary to avoid misunderstanding.
A	181-184 (regulatory requirements)		Guidance should differentiate between specifications that govern product quality and alert limits or other control type limits that provide tighter control but do not present as the only acceptable ranges for the characteristic.	In-process specifications should be based on what is known to produce acceptable quality product, not process variability estimates.
A	189 (regulatory requirements)	Experience	Results and experience.	This is to be specific for the actual production AND operator comments
A	189 (regulatory requirements)	…experience is periodically reviewed…	Need to add expectation that this review is documented and define if expectation is an Annual Product Review element	

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Category	Line No.	Current Text	Proposed Change	Rationale
A	189 (regulatory requirements)	...product performance and manufacturing experience be periodically reviewed…	...product performance and manufacturing experience be periodically reviewed and documented in an Annual Product Review.	Link the periodic review with a document to demonstrate evidence of completion.
A	190 (regulatory requirements)	Ongoing feedback about product performance is an essential feature of process maintenance	Ongoing feedback about product performance is an essential feature of a continuous improvement program	Consistent with Q10 and avoids performance is an essential feature of a continuous improvement program
A	208-212	"Good project management" is described to ensure uniform collection and assessment of information.	Please clarify if an implementation of the "project management" is not a mandatory requirement for a new proves validation. If the answer is yes, please also clarify if effectiveness of the project management is not a subject matter at PAI and periodical inspection.	For better understanding
A	208-218		Consider removing discussion on team member expertise and good project management activities.	The infrastructure considerations for effective execution of a validation program should be left to the firm.
A	208		It is recommended to include a reference to knowledge management as an enabler of the pharmaceutical quality system as outlined in ICH Q10.	

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Category	Line No.	Current Text	Proposed Change	Rationale
A	208-212		"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."	It is recommended to revise the verbiage in this section of the guidance for clarification.
A	210 (general considerations)	These practices should ensure uniform collection and assessment of information	These practices should ensure systematic collection and assessment of information	Replace uniform with systematic. The development process may not be amenable to a uniform approach and it doesn't matter as long as it is methodical
A	210 (general considerations)		'…should ensure ~~uniform~~ collection…'	There might be different ways to collect data at development versus commercial manufacturing
A	211		Consider replacing 'chance' with 'need'	The work 'chance' seems to be inappropriate, in that most redundant information gathering and analysis will come from poorly designed and poorly documented experiments, not from inadvertent duplication of lab studies.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	211 (general considerations)	.., reduce the chance for redundant information gathering and analysis,..	These practices should ensure systematic collection and assessment of information and enhance the accessibility of such information later in the product lifecycle	Delete this portion of the sentence. Good science may actually require redundant information e.g. as confirmatory experiments. In any case it is a company's decision whether they do this or not.
A	214 (general considerations)	..expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, and quality assurance. Project Plans…	…expertise from a variety of disciplines. Project plans	Titles are not universal to all companies (some have validation disciplines). In some small companies a single person or department might fulfill multiple of the example roles suggested.
A	214-217		"We recommend an integrated team approach to process validation that includes expertise from a variety of disciplines to allow for a more comprehensive review."	It is recommended to revise the verbiage in this section of the guidance for clarification.
A	216-217		"Project plans are essential elements for success."	It is recommended to revise the verbiage in this section of the guidance for clarification.
F	214-217 (general considerations)	We recommend an integrated….	Remove the paragraph. The paragraph implies that there is a regulatory requirement to have a documented project plan.	The document shouldn't be used to discuss project management principles or industry functional roles.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	215		Include Process Development, Product Development or Process Sciences as part of the team	The Integrated team approach mentioned does not include departments usually associated with process validation
A	215 (general considerations)	…including process engineering, industrial pharmacy, analytical chemistry….	…which could include as appropriate….	Not all companies may have all the disciplines that are mentioned, nor might it be appropriate to include all of them in process validation. It should be left to the company to compile their team and justify their decision
A	215 (general considerations)	…variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry…	Consider adding…development…as a group; "process development, process engineering"	In many industries the process validation effort is led by process development.
A	215 (general considerations)	Including	For example	Not an all inclusive list so it should be examples
F	216-7 (general considerations)	Project plans… for success.	Delete this sentence	It is not within FDA purview to prescribe how industry should manage the development process.
A	216 (general considerations)		Suggest to add: '… and quality assurance, *as appropriate*.'	

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Category	Line No.	Current Text	Proposed Change	Rationale
F	217 (general considerations)	Project plans, along with the full support of senior management, are essential elements for success.	Effective project management, along with the support of senior management are elements for success.	Individual project plans may not be needed for all validations. Simple changes to a process might be effectively managed under the protocol itself or within Change Management.
A	219 (general considerations)	various studies can be initiated to discover, observe, correlate, or confirm information about the product and process	Clarification	It should not be the intent to encourage "discovery" studies in Phase 3.
A	219-222 (general considerations)		Delete this sentence	This paragraph is too prescriptive regarding how industry should perform development studies.
F	228 (1.a.) 29 1(1.b) (Stage 1- PKU)	It is not clear how to disclose the plan, implementation and results in Stage 1 to FDA.	Please clarify the procedure to disclose to FDA.	Is it acceptable to set out NDA dossiers? If not acceptable, please let us know other way.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	228(1.a.)291(1.b) 330(2.a.)369(2.b.) 413(2.c.)454(2.d.) (Stage 1- PKU) (Stage 2 – FUE)	In the case of amendment for formulation change, is it necessary to implement process validation from Stage 1 again?	There is no description of procedure of process validation for formulation change. The definition of re-validation for formulation change disappears in this draft guidance.	The procedure for formulation change should be clarified. Can FDA accept that process validation focused on the change points? We think the following procedure to submit the process validation report to FDA. 1) The results of process validation in Stage 1 mentioned in NDA dossier. 2) The results in Stage 2 are reviewed and approved internally, and FDA checks it during inspection. Can FDA accept the above-mentioned procedure?
A	219-222 (general considerations)	…various studies	Add at the end of the paragraph: Where such studies form the basis for continual improvement and changes to the manufacturing process, once the data have been analyzed, any such changes should be qualified in accordance with a formal validation protocol.	The context of this paragraph is not clear – maybe move to Stage 3 in the next section as a post- process qualification activity

Category	Line No.	Current Text	Proposed Change	Rationale
F	228-289 (Stage 1- PKU-legacy)		Stage 1 – perspectives for documentation of process knowledge and understanding for existing products should be provided. As written, guidance seems to be new-product/process centric.	Stage 1 – clarity should be provided for the expected activities or application of this phase for existing products processes.
A	235 (Stage 1- PKU)		Add after the end of the sentence: This stage must be completed prior to initial of process qualification studies	See earlier comments regarding possibility of confusion as currently written
A	235 (Stage 1- PKU)	a product that meets its critical quality attributes	Clarify whether the "critical quality attributes" is based on the Q8R, or more general meaning like the PAT guidance.	For better understanding of this context.
A	235 (Stage 1- PKU)		Suggest to add: '… critical quality attributes *and critical process parameters in line with the defined control strategy.*'	Facilitate implementation of ICH Q8(R1)
--	237 (Stage 1- PKU)	Generally, early process design experiments do not need to be performed under CGMP conditions		Excellent and fundamental statement - provides higher degree on freedom to gain more knowledge on product in an early stage of the lifecycle.
A	237 (Stage 1- PKU)	Generally,		This is vague – needs more. When do they require CGMP conditions?

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Category	Line No.	Current Text	Proposed Change	Rationale
A	237-238 (Stage 1- PKU)	Early process design experiments do not need to be performed under cGMP condition,	Please clarify what stage of design experiments shall be subject to cGMP condition, or what criteria shall apply for distinction between cGMP and non-GMP conditions.	For better understanding
A	237-243 (Stage 1- PKU)		Include a reference to ICHQ7A	
A	239 (Stage 1- PKU)			What about GEP (to be included)
A	240 (Stage 1- PKU)	Footnote 9: A notice of availability for this draft ICH guidance published in the Federal Register on July 13, 2007(72 FR 38604). When finalized, this guidance will represent FDA's current thinking on this topic.	Q10 is still referred to as a draft, although Q10 reached step 4 in June 2008, meaning that regions would normally implement (step 5) in 6-12 months.	
C	Viral and Impurity Clearance studies (lines 245 – 247, 601-603)	"There are exceptions, however. For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale."	Suggest revise to read "…should be performed under *appropriate* CGMP conditions" 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, and which impurities are intended in scope.	Clarification needed

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Category	Line No.	Current Text	Proposed Change	Rationale
C	245-246 and 601-603	"viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale"	Remove this requirement	This statement is in the Stage 1 process design section and implies that early development work should be done under CGMP which will create unnecessary and high burden – this requirement is fine for Stage 3 PQ, but not stage 1
C	245 (Stage 1- PKU)	Viral and impurity…		How can this be under CGMP? Does this mean documentation? And if so why not related steps?
C	245 (Stage 1- PKU)	Viral and impurity clearance studies (snip) should be performed under CGMP conditions, even when performed at small scale.	Please clarify the requirement in CGMP to perform viral and impurity clearance studies	For better understanding

Category	Line No.	Current Text	Proposed Change	Rationale
C	245 (Stage 1- PKU)	It is mentioned that viral clearance studies should be performed under cGMP conditions. In the "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human" released by the CBER it is stated on page 24 chapter II,C,5,a that virus clearance studies should be performed under GLP (21 CFR, part 58) conditions.	"For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed under cGLP conditions, even when performed at small scale."	There is a disagreement, which should be clarified. What is more appropriate? In the European guideline CPMP/BWP/268/95: "Note for guidance on Virus validation Studies: The Design, Contribution, and Interpretation of Studies Validating the Inactivation and Removal of Viruses" is recommend to perform virus clearance studies under GLP conditions! The draft guideline should consider the option to recommend both cGMP or as an alternative GLP. I personally would prefer to find a recommendation that such studies should be performed under GLP instead of GMP
C	245 (Stage 1- PKU)		Need clarification on impurity clearance	Companies use different approaches to establish impurity clearance. Also, there is a variety of impurities present. It is not clear what this reference means.
C	245-246 (Stage 1- PKU)		Need for full CGMP for clearance studies	Often done at small scale where full CGMP not feasible

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Category	Line No.	Current Text	Proposed Change	Rationale
C	245-248 (Stage 1- PKU)	"There are exceptions, however. For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale. The quality unit should be involved with these studies as is typical during commercial production."	Delete and edit text: For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed following Good Engineering Practices, including a quality unit review and approval of these studies as is typical during commercial production.	During Process Design, viral and impurity clearance studies are typically performed in laboratory / small scale equipment not intended to be commercial CGMP facilities. Following GEP with quality unit review and approval should provide appropriate controls.
C	245-248		"Where a study has a direct impact on drug safety, for example viral and impurity clearance studies, it should be performed under cGMP conditions."	It is recommended to revise the verbiage in this section of the guidance for clarification.

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Category	Line No.	Current Text	Proposed Change	Rationale
C	245 (Stage 1- PKU)	…viral and impurity…	Both sentences should be clarified by inserting "biological" in front of "…impurity clearance studies…". -------- If this is an oversight then my comment is editorial. If FDA meant it to apply to small molecules, then my comment is critical category. -------- Delete this sentence.	I interpret both sentences to say that any & all impurity clearance studies should be performed under CGMP and with the quality unit involved. This is not justified for most "small-molecule" impurities which are generally detectable by multiple validatable analytical techniques. --------- This is required for Bios but not for small molecule. -------- I do not agree (w/245-247) The imposition of cGMP to assess purge of impurities or viral does not add any value to the quality of the study and is unnecessary burden.

Category	Line No.	Current Text	Proposed Change	Rationale
C	Lines 245-248, and Lines 601-602		Remove mention of impurity clearance for reason stated. 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".	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 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

Category	Line No.	Current Text	Proposed Change	Rationale
A	**250 (Stage 1- PKU)**		**'…inputs to the design ~~stage~~ *space*, such as…'**	**Use wording according ICH Q8 & ICH Q8(R1)**
A	**250-259 (Stage 1- PKU)**		**Replace this paragraph or soften it with a simple statement acknowledging that there are several sources of variability associated with process inputs, i.e., material attributes, process variables, equipment tolerances, etc., that in combination can contribute to the robustness of the process and these should be considered in process design.**	This paragraph is too prescriptive regarding the sources of variability.
A	**252 (Stage 1- PKU)**	**Process information available form the product development stage can be leveraged in the process-design stage**		**Delete the sentence. Companies generally develop product and process in parallel so that there is no possibility for separating these two items into discrete steps**

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Category	Line No.	Current Text	Proposed Change	Rationale
A	254 (Stage 1- PKU)	The functionality and limitations of commercial manufacturing equipment should be considered, as well as the contributions of variability by different component lots, production operators, environmental conditions, and measurement conditions in a production setting.	Sources of commercial variability if known should be considered.	Previous sentence acknowledged that the full spectrum of commercial process capability may not be known at this stage.
A	256 (Stage 1- PKU)	Of	To	
A	Lines 118, and 259-262		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".	Clarification on expectation for testing to failure is needed.
---	259-262 (Stage 1- PKU)		Keep this sentence	Fully agree that process should not be tested until failure is observed.
A	260-262 (Stage 1- PKU)		Align with 118	Seems to contradict 118 (validating EOF)

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Category	Line No.	Current Text	Proposed Change	Rationale
A	264– 273	Beginning with "Designing an efficient process…" and ending with "…material quality attributes."	This section describes DOE, multifactorial interactions, and establishing ranges for incoming components and parameters, and should make the connection to the concept of Design Space, described in ICH Q8.	Harmonization and consistency with ICH Q8
B	270 (Stage 1- PKU)		Perspectives on the level of documentation associated with justification of non-significant parameters throughout the design phase would be valuable.	The level of documentation expected for variables judged to be non-significant is not provided. Guidance would be valuable, especially when dealing with "prior knowledge." Some of this is expert opinion, others are derived from general scientific studies, etc.
A	279 (Stage 1- PKU)	And avoid	And <u>also help</u> avoid	It will not avoid problems but will reduce problems
A	267 (Stage 1- PKU)	Multifactorial interactions	Multi-variate	Consistent with ICH terminology
A	272-273 (Stage 1- PKU)		Add operating parameters	
A	284	"It is essential that activities and studies resulting in product understanding be documented."	Suggest revise to read, "It is essential that activities and studies resulting in product *and process* understanding be documented."	Importance of the process as well as the product

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Category	Line No.	Current Text	Proposed Change	Rationale
A	**284-285 (Stage 1- PKU)**	**It is essential that activities and studies resulting in product understanding be documented**	**Any study used to generate product / process understanding that is subsequently integrated into the Product Control Strategy must be adequately documented**	**Clarity**
A	**286 (Stage 1- PKU)**	**…process. For example, manufacturers should document the variables studied for a unit…**	**"variables regarded as significant"…suggest adding a definitions sections where some of these are better defined.**	**ICH Q7 has a definitions section…there is a lot of confusion regarding 'significant variables' and it would help getting a definition in place.**
A	**286 (Stage 1- PKU)**	**Manufacturers should document**	**Manufacturers and/or developers**	**Not all manufacturers will engage in this on their own but in conjunction with developers (e.g. contract manufacturers)**
A	**286 – 287 (Stage 1- PKU)**	*Guidance: For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as* ***significant.***	**Guidance should utilize terminology which is consistent with guidance on upstream activities (e.g. QbD) so that there is full understanding.**	The guidance does not speak to "critical" parameters nor controls (CPPs/CIPCs). Is it inferred that an additional set of parameters, in addition to some that may be considered acceptance criteria should be highlighted for the purposes of continuous monitoring?
A	**287 (Stage 1- PKU)**	**This information is useful…**	**This data may prove invaluable during….**	**Emphasis – this data can be of very great value to a company and it is in their interest to capture it in documentation**

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Category	Line No.	Current Text	Proposed Change	Rationale
A	287 (Stage 1- PKU)		Suggest to add: '… as significant *in relation to the risk to patient*'	
A	287 (Stage 1- PKU)		Suggest adding: '*Knowledge from* this information…'	Reduce the number of documents and required content from data/information towards knowledge according the 2nd principle of ICH Q9
A	287		"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."	It is recommended to revise the verbiage in this section of the guidance for clarification.
A	289 (Stage 1- PKU)	…or the strategy for control is….		
A	291		"b. Establishing a Control Strategy"	It is recommended to revise the title of this subsection of the guidance to use the term "control strategy" as defined by ICH Q10, as creation of additional terminology may be confusing.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	291 – 315 (Control strategy)	"Section b. Establishing a Strategy for Process Control"	It would 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 Q8 (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.
A	291-296 (Stage 1- SPC)		Add after line 296" use of a HACCP can be useful in defining control strategies	Provide more suggestions on how to accomplish new requirements
A	291 (Stage 1- SPC)	Establishing a Strategy for Process Control	Establishing a Product Control Strategy	Consistency with ICH and avoid introduction of novel terminology that is not defined – Process Control Strategy is not a term currently in use
A	295-296 (Stage 1- SPC)	Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.	For input parameters that have a direct impact on product quality attributes (outputs), strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.	Not all input parameters have an impact on quality attributes. Process control strategies for input parameters without quality impact can require input variations, e.g. to adjust process times depending on the batch size.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	301-306	Special attention to control of the process through operational limits and in-process monitoring is essential (1) where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination), or (2) when intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified. These controls are included in the master production and control records (see 21 CFR 211.186(a) and (b) (9)).	Clarify	It is unclear to us what this really means. Please clarify in more detail.
A	302-303 (Stage 1- SPC)	(1) where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g. viral clearance or microbial contamination),	(1) where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g. viral clearance ~~or microbial contamination~~),	In most cases microbial contamination is measurable. Propose to delete from the examples.

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Category	Line No.	Current Text	Proposed Change	Rationale
C	303 (Stage 1- SPC)	(e.g., Viral clearance or microbial contamination)	Remove microbial contamination	Microbial contamination is detectable and appropriate sampling methodologies are available
A	304 (Stage 1- SPC)	Products	API	Characterization is primarily for APIs and not finished drug products.
A	305 (Stage 1- SPC)	Cannot be identified	May not be fully identified	As it reads now it is too restrictive
A	308-311 (Stage 1- SPC)		Revise to read: "Advanced control strategies may include process analytical technology (PAT) where real time analysis and control loops capable of adjusting process conditions can maintain process consistency and provide improved measures of control."	These statements are imprecise.
A	311 (Stage 1- SPC)	the approach to process qualification will be different from that for other process designs	Brief explanation of what is different between PAT and other process designs will be needed.	It's not enough for understanding of the point on PAT by quoting the reference (line 313) only.
A	311 (Stage 1- SPC)	Process qualification	Process confirmation	Agreement with the Compliance Policy Guide

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Category	Line No.	Current Text	Proposed Change	Rationale
B	317-318	"The planned commercial production and control records, which contain the operational limits and overall strategy for process control…"	"The planned commercial production and control strategy should be written and documented prior to Stage 2 and confirmed as part of Stage 3"	"production and control records" implies final batch record which would not be written in Stage 1. Rather a control strategy should be developed so that it guides facility design and is checked as part of PQ.
F	318/319 (Stage 1- SPC)	"The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation."		Is it OK once leaving Stage 1, if during qualification there are indications that the design was inadequate – would it be better to revise the design, or would moving back a phase indicate that the Stage 1 process was not robust (i.e. in a bureaucracy already thrown 'over the wall)?

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Category	Line No.	Current Text	Proposed Change	Rationale
A	321, 326, 369, 371 (Stage 2-FUE/PQ)		Most firms use term Process Validation to refer to Stage 2 as described in this guide. I agree that Stage 1 and 3 are also extremely important for lifecycle of PV but would avoid the term PQ.	Concern about the continued use of the terms 'Process Qualification' and 'Performance Qualification' (PQ), which they use interchangeably (Lines 369, 371) in this guide. They used this term in the 1987 guide and it has caused and continues to cause confusion in the industry. In the industry, the term PQ is typically used to refer to system (e.g. equipment, process automation) qualification where multiple systems are tested together to ensure they interact as expected. Depending upon the process, many firms do at least some portion of what they call PQ without making product.
F	321 – 325 (Stage 2-FUE/PQ)		Is FDA proposing that design qualification for new and updated facilities will become an agency reviewable deliverable?	Is FDA proposing that design qualification for new facilities will become an agency reviewable deliverable? If I understand correctly, this has typically not been the case.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	323 (Stage 2-FUE/PQ)	…the process design is confirmed…	… the process is demonstrated…	Delete "design." It is the process itself that is being validated not the design.
A	323 (Stage 2-FUE/PQ)	Process qualification	Process confirmation	Agreement with the Compliance Policy Guide
F	323-326 (Stage 2-FUE/PQ)	During the process qualification stage of process validation, the process design is confirmed as being capable of reproducible commercial manufacture.	In light of the guideline of ICHQ8, it seems that information on the commercial process which provides high degree of assurance for consistent production of quality product, shall be described in NDA/PLA documents. In this regard, it is reasonably considered that NDA or PLA shall be filed after PQ is completed. Please confirm this is correct. In the meantime, if FDA could accept the NDA/PLA without any information on PQ data, please clarify what conditions or information would be for this purpose. For example, I was wondering if PQ protocol be required? Please clarify.	

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Category	Line No.	Current Text	Proposed Change	Rationale
F	324-326 (Stage 2-FUE/PQ)	This stage has two elements: (1) design of the facility and qualification of the equipment and utilities, and (2) performance qualification (PQ).	Focus stage 2 on process qualification. Describe 2.a. as process validation prerequisites. Add sentence that before process qualification is initiated it should be verified that all prerequisites are fulfilled to ensure that the process can be operated in the facility using established equipment and utilities.	Facility and process should be decoupled. Facility design and qualification of utilities and equipment are process validation prerequisites, but typically separated from the process validation effort. Facilities are often in operation since years or even for decades when a new process is introduced into the facility. Equipment operating ranges can not be tested for a process that does not exist at the time the facility is qualified.
A	325 (Stage 2-FUE/PQ)	(1) design of the facility and qualification of…	(1) qualification of the facility , equipment and utilities	Clarity. Avoid confusion that may arise from the use of the word “design”
A	326 (Stage 2-FUE/PQ)	Performance Qualification (PQ)	Change term to process qualification. Performance qualification is an established term for a phase in equipment qualification.	
A	326 (Stage 2-FUE/PQ)	Performance qualification (PQ)	Performance confirmation (PC)	Agreement with the Compliance Policy Guide

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Category	Line No.	Current Text	Proposed Change	Rationale
A	326-327 (Stage 2-FUE/PQ)		Need to clarify that the cGMP compliant part refers to large scale operations	In biotech, most of the data in the PQ stage comes from small scale studies. These are not run in cGMP compliant fashion.
A	328 (Stage 2-FUE/PQ)		Revise to read: "Products manufactured during this stage, if acceptable, can be released to the commercial market."	This statement is imprecise.
A	328 (Stage 2-FUE/PQ)	Product manufactured during this stage, if acceptable, can be released.	Batches of product manufactured during this stage may be released after completion of the PQ and sign-off as to the acceptability of the results of the process validation.	Clarity and consistency with line 567. As currently written this sentence could be taken as advocating concurrent release.
A	328 (Stage 2-FUE/PQ)	Stage, if acceptable, can		Needs clarification as to when product may be released – after completion of the PQ
A	328 (Stage 2-FUE/PQ)	"Products manufactured during this stage, if acceptable, can be released".	Add additional text : Products manufactured during this stage, if acceptable, can be released subsequent to marketing approval provided the product was manufactured in accordance to the approved PQ protocol.	Additional text provides clarity as to the intent of this statement.
A	328 (Stage 2-FUE/PQ)	Products manufactured during this stage, if acceptable, can be released.	Please clarify who judge "acceptable" by what data.	For better understanding

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Category	Line No.	Current Text	Proposed Change	Rationale
A	332 – 337 (Stage 2- FUE)		How does the FDA term of "qualification" differ from ASTM's terms of "verification" . Reconciliation of terms is recommended.	Refers to qualification of equipment. ASTM has proposed moving away from this terminology. Does this mean that the ASTM nomenclature is not recognized?
A	333 (Stage 2- FUE)	It is essential that activities to assure proper facility design and commissioning precede PQ	Eliminate	Commissioning is a good engineering practice and is not required under 21 CFR part 211, subpart C
A	334 (Stage 2- FUE)	…performed to assure proper facility design and commissioning precede PQ.	"commissioning"…the earlier statements indication qualification prior to PQ. This statement indicates commissioning. Replace "commissioning" with 'qualification'	Consistency to ensure that the gate to PQ is completed qualification of equipment and utilities
A	335, 341, 345, 349, 357, 372, 445, 559 (Stage 2- FUE)		Add facilities, automation, utilities, and equipment	Need to include all systems: facilities, automation, utilities and equipment since requirement for all of these are the same.
A	336		"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*."	As ASTM E 2007 uses the term "verification", it is recommended to revise the terminology to better align with regulations.

Category	Line No.	Current Text	Proposed Change	Rationale
F	338 (Stage 2- FUE)		Suggest adding: 'It has been assured during the technical transfer that the Control Strategy is comparable or may need to be adjusted.'	The equipment at commercial manufacturing site is not the same as in a development site.
A	341 (Stage 2- FUE)	Selecting utilities and equipment construction materials….	Delete the paragraph or revise to read: "It is an essential pre-requisite to the successful qualification of facilities, systems and utilities that they are selected to be appropriate for their specific use. This requires appropriate design control over materials of construction, selection of appropriate operating principles and performance characteristics.	Clarity. As presently written industry might interpret this as meaning that the selection of these items is part of validation rather than a precondition for purchasing.
A	335 (Stage 2- FUE)	…undertaken to demonstrate that utilities and pieces of equipment are suitable for their	Suggest changing the term "pieces of equipment" to "equipment"	For consistency with the terminology used throughout this section of the document.

Category	Line No.	Current Text	Proposed Change	Rationale
A	**339-349**		**line 341: *Design Qualification: Selecting…*** **line 345: *Installation Qualification: Verifying…*** **line 349: *Operational Qualification: Verifying…***	***Qualification of utilities and equipment generally includes the following activities (…)*** **The different qualification steps are described comprehensively. For clarification purposes the terms "DQ, IQ and OQ", should be incorporated.**
F	**349-352 (Stage 2- FUE)**	**Verify 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.**		**In an existing facility routine production processes for future products are unknown. Consequently operating ranges are not known at the time the facility is qualified. For existing multi-product facilities, typically in stage 1 a process is developed to fit into an existing facility, not the other way around.**

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Category	Line No.	Current Text	Proposed Change	Rationale
A	354-355 (Stage 2- FUE)		Change sentence to, "The process control strategy should be demonstrated to maintain process parameters within defined limits" and don't put a time or quantity limit on it.	Demonstrating that operating ranges should be shown capable of being held as long as would be necessary during routine production could be dicey. The expectation should not be for having data for a run of "X" hours. The control strategy for maintaining process parameters within operating ranges should be demonstrated to be robust and (dare I say) validated. As written, it could be a big problem for continuous manufacture where once the process reaches the steady state, the duration it is run at should be inconsequential.
A	354 (Stage 2- FUE)	…as long as would be necessary during routine production.	…long enough to provide an adequate challenge to the equipment	Some lines run continuously, would we then have to do 24 hour line trials?
F	354-355 (Stage 2- FUE)		Please delete lines 354-355 or move to section b. Performance Qualification, perhaps following the sentence ending on Line 375.	Qualification of equipment should demonstrate operation representative of manufacturing conditions and use.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	354-355 (Stage 2- FUE)	Operating ranges should be shown capable of being held as long as would be necessary during routine production	Confidence that the operating ranges are capable of being held as long as would be necessary during routine production	Not realistic to expect equipment to run as long as a production run in an OQ phase. If this could be in conjunction with confirmation runs then acceptable but implication is that this is prior to confirmation runs.

Category	Line No.	Current Text	Proposed Change	Rationale
F	354 (& 559) (Stage 2- FUE)			Sentence 354 (part of the discussion of qualification) "Operating ranges should be shown capable of being held as long as would be necessary during routine production". As a simple example, in the past for a tank heating system we would show the vessel as capable of meeting the desired temperature and then holding it for a short period of time, say 30 minutes. This now means we would have to hold the temperature for whatever the proposed process time was, say 10 hours. This really would have an impact on the length and cost of qualification. Paragraph beginning at sentence 559- This implies the need for requalification of equipment is based on the results of maintenance and calibration.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	354-355 (Stage 2- FUE)	"Operating ranges should be shown capable of being held as long as would be necessary during routine production"	Delete sentence	The previous paragraph, lines 349-353, clearly captures the true requirements for utility systems and equipment qualification. This requirement is better demonstrated during Performance Qualification.
A	354-355		"Operating ranges should be shown capable of being maintained as would be representative of routine production."	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, it is recommended to revise the verbiage in this section of the guidance.
A	357-367			It is recommended to remove the verbiage in this section of the guidance and refer to ICH Q10 in terms of the change management element.

Category	Line No.	Current Text	Proposed Change	Rationale
F	357 – 366 (Stage 2- FUE)		Guidance should clarify that complex projects which require the use of project validation plans or/and an overall project plan would require the elements noted in 357 – 366.	Not all qualification activities need to be covered in individual plans or overall project plans. An example would include simple pieces of equipment to replace existing like-units that may be inoperable. Guidance should be clarified.
A	359 (Stage 2- FUE)	Certain		Delete "Certain" since it leaves it too open and vague, or put in an example of what activities need to be prioritized (why not all?)
F	360-363 (Stage 2- FUE)	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.	Delete and edit text: The plan should identify (1) the scope of testing and assessment of outcomes (2) roles and responsibilities, and (3) the procedures for documenting and approving the qualification.	Would suggest the Qualification project plan be a high level document, equivalent and incorporated into a project Master Validation Plan. Items 1, 2 and 3 are details best documented in the individual commissioning/qualification protocols.
A	364 (Stage 2- FUE)		'… for the ~~evaluation~~ *assessment* of changes.'	Using ICH Q9 definitions consistently

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Category	Line No.	Current Text	Proposed Change	Rationale
A	366 and 413		Proposal to use only one unambiguous term, suggested term: protocol	*The quality control unit must review and approve the qualification plan and report.* *Performance Qualification protocol.* Please clarify whether the terms "plan" and "protocol" are meant to be interchangeable in the context of this draft guidance.
A	366 (Stage 2- FUE)	Quality control	"Quality unit" or "Quality Assurance"	Quality control is typically the labs. Quality assurance is the oversight.
A	369(2.b.) 13(2.c.) 454(2.d.) (Stage 2- PQ)	If the results of 3 batches in PQ meet criteria, is it acceptable to continue confirmation of quality in Stage 3 until the batch number reach to numbers to be able to confirm quality statistically?	The border of transition from Stage 2 to Stage 3 is not clear.	The continuity between concept and actual practice for current guidance and new draft guidance should be clarified.
F	369(2.b.)413(2.c.) 454(2.d.) (Stage 2- PQ)	The timing of "Pre-approval Inspection (PAI)" and of completion of PQ in prior approval supplement is not shown in this guidance.	Though this guidance states "This guidance does not specify what information should be included as part of a regulatory submission", we expect additional descriptions on the timing of PAI that the Agency assumes.	Does the Agency assume that a PAI is to be conducted just after the completion of PQ?

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Category	Line No.	Current Text	Proposed Change	Rationale
F	369(2.b.)413(2.c.) 454(2.d.) (Stage 2- PQ)	If Pre-approval Inspection (PAI) is conducted after the completion of PQ, can we release the PQ batches before PAI?	The timing of PAI and batch release is not clear.	The timing of PAI and release of PQ batches should be clarified.
F	369(2.b.)413(2.c.) 454(2.d.) (Stage 2- PQ)	The relation between the PQ performing and the change in approved NDA and ANDA(Prior approval supplement, CBE30, Annual report) is not clear.	Please clarify the relation between the PQ performing and the change in approved NDA and ANDA(Prior approval supplement, CBE30, Annual report).	Validation and change in NDA/ANDA are closely related.
A	370 (Stage 2- PQ)	Process qualification	Process confirmation	Agreement with the Compliance Policy Guide and eliminate ambiguity with performance qualification studies run for utilities
A	371-374 (Stage 2- PQ)		Align Lines 371-374 with 383 and 390.	Appears to put emphasis on commercial scale during PQ, although some flexibility is allowed (Lines 383-390) to consider data from other studies (e.g. small scale, and previous experience with similar products/processes) depending on scale dependencies (if any). These sections appear to be a bit conflicting.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	371 (Stage 2- PQ)		Align definition of PQ more closely to ICH Note: Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications (ICHQ7A)	Is FDA's definition sufficient close to ICH; possible to refer back to previously used terminology, e.g. consistency batches, to avoid misunderstanding
A	371 – 372 (Stage 2- PQ)		Line 372 indicates that a facility is qualified. Recommend changing to indicate that a facility is commissioned.	Implies that facilities need to be qualified. Clarify that facilities are commissioned
A	371-411 (Stage 2- PQ)	Stage 2, Performance Qualification Approach section	Additional detail regarding what is expected from a PQ when using PAT is needed.	
A	374 (Stage 2- PQ)	A successful PQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected	A successful PQ will provide documented evidence that the designed process is capable of consistently producing commercial product meeting its critical quality attributes and performance characteristics.	Clarity and consistency with ICH guidance

Category	Line No.	Current Text	Proposed Change	Rationale
B	374 – 375 (Stage 2- PQ)		Original validation guidance prescribed that the PQ runs be conducted at worst case conditions. This document is silent in this regard. The preferred approach is to run at normal operating conditions and set points and use earlier phase (prePQ) experience to support the ranges.	
B	379	The decision to begin commercial distribution should be supported by data from commercial batches	The decision to begin commercial distribution should be supported by data from commercial batches and at least accelerated stability study should be completed, without significant changes (ICH, stability testing of new drug substances and products Q1A(R2))	The proposed shelf life should be defined prior the product distribution.
B	379		"The decision to begin commercial distribution should be supported by data from commercial validation batches."	It is recommended to clarify the verbiage in this section, as data from commercial batches cannot be accumulated prior to a decision to distribute commercially.

Category	Line No.	Current Text	Proposed Change	Rationale
B	379-380 (Stage 2- PQ)		Change to batch(es). Suggest that this sentence be changed to: "The decision to begin commercial distribution should be supported by data from at least one commercial batch."	There is an effort to get away from the "3 batch mentality" but this sentence requires data from commercial "batches". If this is held in practice, the best we have gained is qualification from three batches to two batches at full scale. If we have data from small scale experimentation and a robust scalability, then one confirmatory batch at full scale should suffice.
B	379-380 (Stage 2- PQ)	"The decision to begin commercial distribution should be supported by data from commercial batches."	The decision to begin commercial distribution should be supported by data from commercial-scale batches.	Batches that are produced at commercial-scale meeting all pre-requisites but used in clinical studies instead of commercial distribution should also be allowed to be used in the Performance Qualification. Changing "commercial batches" to "commercial-scale batches" allows for this.

Category	Line No.	Current Text	Proposed Change	Rationale
B	379 – 380 (Stage 2- PQ)		This statement should be changed to state that the decision to begin commercial distribution should be made from data from commercial ***scale*** batches produced under normal commercial conditions.	This sentence suggests that the decision to begin commercial distribution has to be made on "commercial batches". But development and pre-commercial batches could be made under commercial conditions and should be able to be used.
F	380 (Stage 2- PQ)	Data from laboratory and pilot studies can provide additional assurance.	Data from laboratory and pilot studies can be used to provide initial process qualification and may justify reducing the number of commercial batches needed to demonstrate process consistency. Where such an approach is used it should be based on a documented risk assessment	The idea of a lifecycle process validation is that it enables companies to do better work during development resulting in less work at the commercial stage. This approach is consistent with ICH Q8,9, 10 principles
A	380-381 (Stage 2- PQ)		Delete this sentence.	This statement is imprecise.
B	383 (Stage 2- PQ)	The approach to PQ…	Description of differences on PQ approach between development without QbD and with QbD will be needed.	Relation of Q8 is not clearly explained in this context.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	385, 389 and 403 (Stage 2- PQ)		Please revise from "commercial batches" to "commercial-scale batches" or "production/ production-scale batches" in Lines 385 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.
A	385 (Stage 2- PQ)		Insert "scale" into "commercial batches," since at this stage the material may come from non-saleable materials.	
A	386 (Stage 2- PQ)	…to establish the manufacturing conditions in the PQ	…to establish the manufacturing conditions in the batch manufacturing instructions	Clarity. This can confuse the reader who may be (mis)led to believe that manufacturing conditions in PQ can be different to those in routine commercial

Category	Line No.	Current Text	Proposed Change	Rationale
A	**386 (Stage 2- PQ)**		**'… should be ~~used~~ *considered* to establish….'**	**These data / information may not be <u>used</u>, because they may represent a slight different process before filing. However this data/information may provide good understanding of a specific event/problem.**
A	**389-392**		**"Previous experience with similar products and processes can also be considered."**	**It is recommended to revise the verbiage in this section, as this sentence as written could lead to confusion around what is 'credible' and what is 'sufficiently similar'.**
B	**391 (Stage 2- PQ)**		**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."**	**The draft guidance encourages the 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 commercial scale lots have bee produced.**

Category	Line No.	Current Text	Proposed Change	Rationale
B	391, 429, 437 (Stage 2- PQ)		Soften language in text to allow for more flexibility. Lines 429 and 437: delete "statistical" since it is only given as an example in Line 391.	There is an emphasis on use of statistical methods (e.g. Lines 391, 429, 437). This typically means at least 6-10 data points, if not more. Generally I support that approach and for some projects we have the data. However, for many projects we would not typically plan on 6 PQ lots, which would be what we need for statistical analysis between lots as described in Lines 429/437
B	394-395	In most cases, PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance.	Specify what the level of sampling is higher than.	It is unclear what the higher level of sampling in PQ is compared to
B	394-396 (Stage 2- PQ)	"In most cases, PQ will have a higher level of sampling…" (Stage 2) "We recommend continued monitoring and/or sampling at the level established during the process qualification phase until sufficient data is available…"	There needs to be a definition of how much sampling is appropriate and for how long.	It would be difficult to justify an aggressive sampling program during protocol execution, if the organization needs to maintain that sampling plan into commercial production for a length of time.

Category	Line No.	Current Text	Proposed Change	Rationale
B	394-397, 533-535 (Stage 2- PQ)		Qualify in text that a higher level of sampling MAY be (or 'is typically') necessary during PQ phase, depending upon the process. Also state in Lines 397, 533-535 that a higher level of sampling after PQ may be needed depending upon the process, and the knowledge about that process (e.g. its critical parameters/attributes). ------ Delete sentence OR rewrite with the option to decrease the level of testing if justified by process knowledge, robustness and capability	A 'higher level of sampling/testing' during the PQ phase (Lines 394) is specified. This may or may not be needed depending upon the step and critical attributes of a given process. The draft goes on to state that this higher level of sampling should continue after the PQ phase (Lines 397, 533-535) which is not necessarily what we are doing now and may not be necessary depending upon the given step/process. --------- This statement sounds like there will be no relief from intensified sampling over the product lifecycle. As more confidence is obtained in the process and robustness and process capability is demonstrated, reduced testing should be allowed, if justified by the ever increasing process knowledge obtained for the product

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Category	Line No.	Current Text	Proposed Change	Rationale
B	391-392 (Stage 2- PQ)	Please explain in detail what "statistical metrics" means.	Please clarify the definition or examples of "statistical metrics".	The definition or examples of "statistical metrics" is needed for concrete action planning.
B	394-398	Sampling & additional testing during 'PQ' and during on-going verification. As written, the text does not seem to take account of the development knowledge and the process monitoring.	Modify to reflect that increased sampling &/or testing *may* be required until on-going verification stage.	For a process developed by QbD principles and with a thorough process understanding prior to validation, additional sampling & testing should be commensurate with the level of knowledge and the effectiveness of the control strategy.
B	394-395		Please add 'than commercial manufacturing' at the end of the sentence or otherwise complete the sentence.	Sentence seems to be incomplete, with an implied comparison.
B	395-396 (Stage 2- PQ)	The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch processing.		This concept fits for many drug product processes, e.g. tablet production or aseptic filling. In an API process, product quality changes during batch processing, e.g. due to impurity removal etc. so that the product quality cannot be uniform during the batch processing.

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Category	Line No.	Current Text	Proposed Change	Rationale
B	396 (Stage 2- PQ)	This greater level of scrutiny accompanied by a higher level of sampling should continue through the process verification stage, as appropriate	Upon completion of this stage of the process qualification, data should be analyzed and decisions made regarding appropriate activities for ongoing process verification.	Clarity. Process validation is a lifecycle activity. As presently written is seems as if FDA is requiring the same level of sampling (usually very high) generally taken during PQ throughout routine commercial manufacturing.
B	'Commercial Batches' (lines 396, 379)	Term is used without definition. Clarify if it intended to mean 'commercial *scale* batches' or 'batches intended for commercial sale'	Clarify that data from commercial scale is not actually required before 'PQ' batches, but if available is useful and may be advisable depending on the product & process.	Clarification needed.
B	396	This greater scrutiny accompanied by higher level of sampling should continue through the process verification stage, as appropriate		Why do we need to have higher level of sampling through the process verification stage? It is recommended to used risk based approached for sampling
B	397 (Stage 2- PQ)		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."	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.

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Category	Line No.	Current Text	Proposed Change	Rationale
B	398 (Stage 2- PQ)		Suggest to add: 'Risk assessment could be used for a better understanding of the impact	Facilitate to use ICH Q9 principles (1st principle)
A	397-398 (Stage 2- PQ)	Process verification	Process confirmation	Eliminate new expression and Agreement with the Compliance Policy Guide
A	400-403	The extend to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.	The extend to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be validated in relevant laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.	The final confirmation of re-use studies is usually achieved several years after initial commercial production. Hence, as lifetime validations wouldn't be completed for years, the performance qualification (line 377-378) wouldn't be completed prior this duration.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	400-403	The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture."	Delete and edit text: The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies, and verified during PQ. Extensions and demonstration of their usable lifetime should be confirmed by concurrent validation during commercial manufacture.	Flexibility should be provided to demonstrate the usable lifetime of a component post PQ during commercial manufacturing and supply.
B	402-403	The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant Laboratory studies and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.	…confirmed through continuous process verification during routine production.	This kind of continuous process verification is called for in the document as outlined in the description of Part 3. Presently such ongoing validation work is commonly performed as part of a concurrent validation. This is not run with an SOP but rather by monitoring routine production. This re-wording brings common practice in alignment with the new paradigm.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	402 (Stage 2- PQ)		Insert "concurrent" before "PQ".	Clarify allowance for concurrent studies in column lifetime studies
A	402 (Stage 2- PQ)		'… by an ~~ongoing PQ protocol~~ *CPV* during commercial…'	Potential source for misunderstanding / interpretation: Be consistent with chapter II: As described the PQ is continued towards continued process verification.
A	402-403	The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.	…confirmed through continuous process verification during routine production.	This kind of continuous process verification is called for in the document as outlined in the description of Part 3. Presently such ongoing validation work is commonly performed as part of a concurrent validation. This is not run with an SOP but rather by monitoring routine production. This re-wording brings common practice in alignment with the new paradigm.
A	405 (Stage 2- PQ)		Add CQV	Mention 'Continuous Quality Verification' to use terms consistent with other Industry Standards (e.g. ASTM)
A	408-409 (Stage 2- PQ)	Process qualification	Process confirmation	Agreement with the Compliance Policy Guide

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Category	Line No.	Current Text	Proposed Change	Rationale
A	413 (Stage 2- PQ Protocol)	Performance Qualification	Performance confirmation	Agreement with the Compliance Policy Guide
A	417 (Stage 2- PQ Protocol)		Insert "or reference" at end of line 417.	Protocol should either contain bullets or be able to reference that information in another document.
A	422 (Stage 2- PQ Protocol)		'…it will be ~~evaluated~~ *assessed*.	Using ICH Q9 definitions consistently
A	424, 449-450	Use of term 'Characterization tests'	Clarify what is intended.	Clarification needed
A	424 (Stage 2- PQ Protocol)	(in-process, release, characterization)	(e.g. characterization for APIs, in-process and release tests for drug products)	Clarify expectations between API and drug product
A	425		"Tests to be performed (in-process, release, characterization) and acceptance criteria for each critical processing step."	It is recommended to revise the verbiage in this section of the guidance for clarification.
A	425 (Stage 2- PQ Protocol)		Suggest to add bullet: 'Link to control strategy, if a QbD type approach is used'	Facilitate implementation of ICH Q8 & ICH Q8(R1)
E	427 (Stage 2- PQ Protocol)		Add 'storage of samples"	It is common to specify storage requirements for samples

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Category	Line No.	Current Text	Proposed Change	Rationale
A	427-432		"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 statistical confidence of quality. 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."	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. It is recommended to revise the verbiage in this section of the guidance.
B	428 – 429 (Stage 2- PQ Protocol)		Balance statistical sampling schemes with the material characteristics/form at the process step.	Some sampling locations cannot be sampled adequately to provide sufficient statistical confidence (i.e. top and bottom of tank samples)

Category	Line No.	Current Text	Proposed Change	Rationale
B	**428- 430**	**The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.**	**Maybe include wording that allows data from other sources in addition to the PQ data to provide confidence in batch to batch variation.**	**Depending on the interpretation a relatively large number of batches could be needed to estimate the batch-to-batch variation with sufficient statistical confidence at PQ**
B	**Statistical Methods (429, 437, 430, 535)**	**There are several references to the use of statistical methods and analysis. (statistical confidence (429), statistical methods (437), confidence levels (430), variability estimates (535) and similar terms).**	**Clarify/provide examples on what degree of statistical scrutiny is expected (e.g. calculation of Cpk, assurance of 95% confidence levels, etc)**	**Expectation may be over-interpreted.**
A	**430 (Stage 2- PQ Protocol)**		**'… based on risk ~~analysis~~ *assessment*'**	**Using ICH Q9 definitions consistently**

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Category	Line No.	Current Text	Proposed Change	Rationale
A	431	Sampling during this stage should be more extensive than is typical during routine production	Change "should" to "could"	If challenge studies performed before this stage have proven sufficient process understanding and the establishment of a proven process model the PQ will merely serve as a verification of the process model in full scale. Increased sampling will not be necessary in all cases as studies earlier can have shown adequate measurements systems to document the quality attributes. The rationales provided in the risk based approach will show this.
B	432 (Stage 2- PQ Protocol)		Add can use risk assessment and to determine extensiveness of sampling; link to patient, stage of mfg	Sampling should be risk based. Number of samples required might reasonably increase as you get closer to the patient
A	437 (Stage 2- PQ Protocol)		Suggest adding: 'A description of *or reference to* the statistical method…'	

Category	Line No.	Current Text	Proposed Change	Rationale
B	437-439 (Stage 2- PQ Protocol)	A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter batch variability).	A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metric defining inter batch variability and intra-batch variability, where appropriate.	Analysis of intra- and inter batch variability makes sense for drug product processes. For many API processes, e.g., biotech MAB purification, process intermediates are homogeneous solutions, where intra-batch variability testing makes no sense.
A	445 (Stage 2- PQ Protocol)			Move the paragraph to line 419 before process is discussed since this activity needs to precede process qualification
F	445-447 (Stage 2- PQ Protocol)	Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources, if not previously accomplished.		Facility, utilities and equipment qualification are process qualification prerequisites and should not be part of the PQ (process qualification) protocol. Personnel training is a GMP requirement and should be overseen by the firms quality system and thus not be included in a PQ protocol.
B	(Stage 2- PQ Protocol)		Does the guidance allow for non-completion of pre-requisites prior to final approval of the protocol?	The elements described in this section should already be completed prior to protocol approval.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	456		Change “appropriate” to “relevant”	Protocol and report should be reviewed and approved by all appropriate departments.
A	458 (Stage 2- PQ Report)	…protocol	Or SOP	Change control is usually in an SOP not a protocol
A	449-450 (Stage 2- PQ Protocol)	"Status of the validation of analytical methods used in measuring the process, in process materials, and the product."	Edit text: Verify the validation of analytical methods used in…”	Validation of analytical methods should be a pre-requisite to process PQ.
F	459-460 (Stage 2- PQ Report)	Such departures (from the protocol) must be justified and approved by all appropriate departments and the quality unit before implementation.	Major departures (from the protocol) must be justified and approved by all appropriate departments and the quality unit before implementation. Minor departures from the protocol can be reported and assessed in the report.	There are always minor discrepancies to the protocol. Prior approval of every minor change to the protocol before implementation is unrealistic. CFR 211.100 (b) states "Any deviations from the written procedures shall be recorded and justified", not that it must be pre-approved.
A	463		“Where the process operating ranges have been justified and previously documented, the PQ lots should be manufactured under normal conditions…”	It is recommended to revise the verbiage in this section of the guidance for clarification.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	469-470 (Stage 2- PQ Report)		Please revise to state: "… should be prepared after the completion of the protocol and prior to commercial distribution of product."	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.
F	472 (Stage 2- PQ Report)	Discuss and cross-reference all aspects of the protocol.	Discuss and cross-reference all aspects of the protocol. Include a complete list of all validated process parameters to be used for routine product release.	A list of complete validated process parameters as part of the report links the validation study and commercial production and product release.
A	474 (Stage 2- PQ Report)		'…Summarize *knowledge gained from* data collected…'	The summary should not repeat what is written elsewhere. The focus should be on conclusions to a fast understanding e.g. by introducing new employees including managers. Use the 2nd principle of ICH Q9
A	476 (Stage 2- PQ Report)		'~~Evaluate~~ *Assess* any …'	Using ICH Q9 definitions consistently
A	479 (Stage 2- PQ Report)		Please revise to delete "all" from the sentence.	It is not necessary to discuss all manufacturing non-conformances and deviations, only those that have potential impact to validity of PQ study.
A	487 (Stage 2- PQ Report)		'… state of *control according the details in filing*. If not…'	Link to regulatory processes

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Category	Line No.	Current Text	Proposed Change	Rationale
A	487 – 491 (Stage 2- PQ Report)			Confusing. Seems to indicate that there may be a possibility to justify release of lots to the market even when a conclusion regarding successful completion of PQ cannot be reached. This would seem contrary to the expectations of successful conformance batch completion prior to distribution as described in CPG 7132c.08.
F	494 (Stage 2- PQ Report)		Suggest to add a bullet: 'Reference to approved final 'master batch record''	This document should recognize all experience and knowledge gained

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Category	Line No.	Current Text	Proposed Change	Rationale
A	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. 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.

Category	Line No.	Current Text	Proposed Change	Rationale
F	495ff (Stage 3- CPV)	Stage 3 Continued process verification		The trending strategy should be differentiated depending on the parameters. Efforts should be focused on critical quality attributes. Verification that the process remains in a state of control (validated state) should verify at first that the validation acceptance criteria from phase 2 are consistently met. Drifts or (more typical) fluctuations within the acceptable range from stage two are not a concern if product quality is not affected.
F	495 (3.:Stage 3)	We assume it is acceptable to submit annual report or report in sorter periodic interval as process validation report in Stage 3. Can FDA accept our proposed procedure?	Please clarify the requirement about the process validation report in Stage 3.	The requirement about reporting format or style of process validation report in Stage 3.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	495 (3.:Stage 3) (Stage 3- CPV)	If you don't accept the annual report as process validation report of Stage 3, please let us know the best way to report the process validation results in Stage 3 to FDA. Is ASTM E2537-07 standard considered to be useful for procedure of process validation in Stage 3?	Please clarify the requirement about the process validation report in Stage 3.	The requirement about reporting format or style of process validation report in Stage 3.
A	495 (3.:Stage 3) (Stage 3- CPV)	Please explain the reason why "Continued Process Verification" is used in this draft guidance. In addition, please explain why FDA uses "Continued", instead of "Continual" or "Continuous".	The relation among concepts meant by each wording and actual operation procedures is not clear.	Please let us know the difference among "Continued", "Continual" and "Continuous". Is there any meaning to use "Continued" against wording in ICH Q10?

Category	Line No.	Current Text	Proposed Change	Rationale
F	**495 – 565 (Stage 3- CPV)**			**Stage 3 -- Continued process verification** • **The reliability of PAT for real time measurement and control of the process should be assessed during Stage 3 under actual manufacturing conditions. It is difficult to do that during Stages 1 and 2. The off-line analytical data need to be collected on a periodic basis during Stage-3 to make such an assessment.** **Process characterization (Stage 1 -- Building and Capturing Process Knowledge and Understanding) is generally carried out in small scale experiments in the laboratory and the results may deviate from commercial manufacturing due to scale. Periodic amendments/updates need to be made to process characterization based on Stage-3 results.**

Category	Line No.	Current Text	Proposed Change	Rationale
A	497 (Stage 3- CPV)	The goal of the third validation stage is…	Description on a position of real time quality control such as PAT in the continued process verification will be needed.	Handling of real time QC data is not clearly described in this context.
A	497-565 (Stage 3- CPV)	Stage 3 – Continued Process Verification	Elaboration regarding what is expected from "process monitoring" and other elements (i.e. human errors, continuous improvement, and facility/utilities/equipment) is needed.	
A	(Stage 3- CPV)	Stage 3 – Continued Process Validation	This will require significant statistical work/monitoring for API. It appears that FDA would expect intra and inter batch statistical monitoring, review, and control on finished API. Typically, most API manufacturers look at the inter batch variation (batch to batch) at most and not the intra (usually only during formal validation activities) variation. Also, additional work related to data monitoring and trending including raw materials will be required as they are likely not being statistical monitored on a routine basis (although probably a good idea).	This may be appropriate for pharmaceuticals but not sure it is truly required for API.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	498-500 (Stage 3- CPV)	A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal.	Please clarify what means the system for detecting unplanned departures from the process as designed. Is this system different from the current deviation control system?	For better understanding
A	502	Not covered	Definition of process drift	Need an understanding of what defines drift within a validated process
A	502		'The ~~evaluation~~ *assessment* should…'	Using ICH Q9 definitions consistently
B	509-511		Add to this section: 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, tools like production quality reviews or production reports are sufficient.	Stage 3 requirements outlined in Section IV.B.3. especially the use of statistical methods, is not applicable for processes that are infrequently and in small batch numbers executed, e.g. 1 to 3 single batches a year. For these processes statistical methods and procedures cannot be used to evaluate process stability and process capability.
A	509-510 (Stage 3- CPV)	The data should be statistically trended and reviewed by trained personnel	Please clarify what trained personnel means? Should this personnel be a statistician or a person trained in statistical process control techniques?	For better understanding

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Category	Line No.	Current Text	Proposed Change	Rationale
A	510 (Stage 3- CPV)	The information collected should verify that the critical quality attributes are being controlled throughout the process	The information collected should demonstrate that the product control strategy consistently ensures that critical quality attributes and product performance characteristics are achieved.	Clarity and Consistent with ICH terminology CQAs are not controlled – process parameters are controlled in order to achieve the CQAs
A	511 (Stage 3- CPV)		'…attribute *and critical process parameters, if appropriate* are being…'	Facilitate implementation of ICH Q8(R1)
A	511 (Stage 3- CPV)		Suggest to add: This could be done using existing procedures e.g. Annual Product Review	Facilitate implementing ICH Q9: Use the 2nd principle of ICH Q9
A	513 (Stage 3- CPV)		Revise sentence to "We recommend the data collection plan include statistical methods and procedures in measuring and evaluating process stability and process capability."	This statement is too prescriptive. FDA should not dictate detailed personnel qualifications. This is redundant to 21CFR 211.25.
F	513 (Stage 3- CPV)		Not necessary to review who should develop data collection plans. The fact that the plans should be statistically based should suffice.	

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Category	Line No.	Current Text	Proposed Change	Rationale
A	519		"Management should ensure the appropriate cross-functional areas review this information. These efforts can identify variability in the process and/or product."	It is recommended to revise the verbiage in this section to be consistent with ICH Q10, where leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.
F	513-521 (Stage 3- CPV)		Please clarify if a data collection plan and statistical method and procedure are mandatory or not. Further, please confirm if deficiency or insufficiency of this statistical system is subject to warning letter or not?	For better understanding
A	519		Change the term "stability" to "robustness" in the following sentence "Production data should be collected to evaluate process stability and capability"	The use of the term "robustness" may be unclear, as the term has traditionally been limited to the evaluation of analytical procedures.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	519 – 521 & 545 – 548 (Stage 3- CPV)		Comment to propose that there should be an organization in place that reviews data for process stability and capability (519 – 521) and that reviews data for trends and drifts, without explicitly mentioning that the Quality department should do this.	The guidance document describes that the Quality Department should do the reviewing of process data for stability and capability of the process and for assessing trends and drifts. There may be other functions in the organization that could exercise this task (better).
F	520-521 (Stage 3- CPV)	This information can be used to alert the manufacturer that the process should be improved.	Please clarify whether the manufacturer need to submit the report in Stage 3 to FDA or not. If necessary, please indicate the procedure how to supply the report to FDA.	For better understanding
A	524 (Stage 3- CPV)		' and/or ~~mitigate~~ *control* strategies..'	Using ICH Q9 and ICH Q8(R1) definitions consistently
A	525 (Stage 3- CPV)	However, a process is likely to encounter…	However, over its lifecycle, a process is likely to encounter…	Clarity
A	Lines 530-531 (Stage 3- CPV)		Please revise to state: "…scrutinize intra-batch, inter-batch and campaign summary data as part of a comprehensive *continued process verification* program."	It is suggested to include additional verbiage describing periodic review of campaign summaries as appropriate where variation might be seen in extended manufacturing campaigns.

Category	Line No.	Current Text	Proposed Change	Rationale
B	**530 – 533 (Stage 3- CPV)**		**Attribute testing of product under the PQ protocol or during post-monitoring using PQ sampling plans may serve as the release testing since the product performance will meet the license requirements.**	▪ **The bridging of release test criteria to performance qualification acceptance criteria should be considered when executing the continued monitoring of batches post PQ. It should not be necessary to additionally test batches which pass PQ criteria testing.** **The burden of testing on the laboratory and additional costs need to be considered in the implementation of such a strategy.**
B	**533 (Stage 3- CPV)**	**We recommend continued monitoring and / or sampling at the level established during the process qualification stage until…**		**Delete the sentence.** **(See comment on line 396).** **It is neither feasible nor desirable for a company to maintain the levels of sampling used during initial PQ on a routine basis except in very specific instances where a parameter is determined to have particular criticality and in this case it would be part of the product control strategy anyway.**

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Category	Line No.	Current Text	Proposed Change	Rationale
A	533-535 (Stage 3- CPV)		Revise end of sentence to read: ". . . to generate significant estimates of risk associated with process variability."	This statement is imprecise.
B	533 (Stage 3- CPV)			Recommendation is to continue monitoring and/or sampling at the same level as during Process Qualification (Process Validation). Once variability is known monitoring/sampling can be adjusted (statistically). This is a recommendation but will have an impact on workload of lab.

Category	Line No.	Current Text	Proposed Change	Rationale
A	533-537			It is recommended to delete the verbiage in this section of the guidance. For assessment of batch uniformity where extensive sampling is performed during stage 1 and stage 2, and where sample bias is a well recognized issue (powder sampling operations), the additional sampling and testing for uniformity in stage 3 may not add value. Additionally the requirement to perform the extensive additional sampling and testing in stage 3 as performed in stages 1 and 2 could prevent companies from performing the additional testing at those stages.
B	533/534 (Stage 3- CPV)	"In most cases, PQ will have a higher level of sampling…" (Stage 2) "We recommend continued monitoring and/or sampling at the level established during the process qualification phase until sufficient data is available…"	"In most cases, PQ will have a higher level of sampling…" (Stage 2) "We recommend continued monitoring and/or sampling at the level established during the process qualification phase until sufficient data is available…"	It would be difficult to justify an aggressive sampling program during protocol execution, if the organization needs to maintain that sampling plan into commercial production for a length of time.

Category	Line No.	Current Text	Proposed Change	Rationale
B	533-534 (Stage 3- CPV)	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.	We recommend continued monitoring and/or sampling at an increased level when compared to standard control until sufficient data is available to generate significant variability estimates.	Process confirmation sampling is excessive for continued operations
B	533-534 (Stage 3- CPV)		Need to provide further clarification on the expectation to monitor at PV level post PV campaign	Testing at PV level is expensive. Number of lots for data to be statistically significant is 30. This would mean increased testing for 4-6 times more runs than what we do today. Is that really what is recommended?
B	533-535 (Stage 3- CPV)	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.	Insert text: We recommend continued monitoring and/or sampling for all Critical Process Parameters and Critical Quality Attributes at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates.	Extended testing and monitoring should be risk based and reserved for parameters and attributes that impact patient health and product quality.

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Category	Line No.	Current Text	Proposed Change	Rationale
B	533-535 (Stage 3- CPV)	Continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates.	Please clarify how much data is required to support sufficiency for significant variability estimates. Is three batch data enough for this purpose?	For better understanding

Category	Line No.	Current Text	Proposed Change	Rationale
B	**(Stage 3- CPV)**		**Ask for clarification of sampling expectation during Stage 3 – Continuous Process Verification**	**The recommendation to continue to monitor and/or sample commercial batches at a level consistent with PQ after PQ until variability is adequately characterized seems excessive and difficult without PAT applications. I could understand maybe a closer review and trending of batch records for the first "X" batches after PQ, but to continue to sample like PQ seems a bit overwhelming - unless I'm misunderstanding this.** **Otherwise, it seems like a clear direction to a lifecycle validation approach is being provided. Conceptually, I think this is good… we'll just need to figure out some of the systems to handle this post-PQ.**
B	**533 -536** **(Stage 3- CPV)**			**I do not agree on maintaining the same levels of PV testing during the verification stage….**

Category	Line No.	Current Text	Proposed Change	Rationale
B	**533 – 537 (Stage 3- CPV)**		▪ **Guidance needs to be clear on how to interpret non-compendial sampling plans and modified acceptance criteria in order to meet compendial release requirements during the continued monitoring phase. For extended monitoring at the level established in the PQ, what is the interpretation of impact to the PQ in the event of a failure? There should be reasonable decoupling of the PQ from the performance monitoring unless it is clear that the failure is inherent to normal variability of the process.**	
A	**536 (Stage 3- CPV)**		**Suggest adding: 'representative level *for the purpose that the risk quality remains controlled.'***	**Facilitate implementing ICH Q9**

Category	Line No.	Current Text	Proposed Change	Rationale
B	536-537 (Stage 3- CPV)	Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly.	The document should elaborate more on the expected review frequency and rationale for the frequency. For example, is annual product review frequent enough? Could some processes need review more or less often than others or less often than annual product review? Can annual product review be adequate to evaluate well established processes with no significant degree of variability historically? What criteria should be used to determine how to set the frequency?	To avoid interpretive subjectivity by agency regulators on how often the review should occur and allow flexibility to selecting review frequency to allow less frequent review for those products with no historical performance issues.
B	537 (Stage 3- CPV)			Periodic re-validation criteria to be defined. This may become a problem for infrequently manufactured products. This may automatically mean that for infrequently manufactured products a higher degree of in-process testing would have to be implemented.
A	539 (Stage 3- CPV)	…defect complaints…	…complaints…	Redundancy – all complaints indicate some type of defect.

Category	Line No.	Current Text	Proposed Change	Rationale
F	541-542		Please delete the sentence 'Production line operators and quality unit staff should be encouraged to provide feedback on process performance.'	The means in which improvement opportunities are gathered and evaluated by management should not be in a guidance document, as it is not likely that all of the feedback will be purely GMP in nature.
F	541-542 (Stage 3- CPV)	Production line operators … provide feedback…		This is an interesting statement. We currently have a limited formal program for capturing such feedback. (…" production line operators and Quality staff should be encouraged to provide feedback on product performance…")
F	543 (Stage 3- CPV)	Operator training	Delete	GMP Issue
F	543-548 (Stage 3- CPV)		Delete sentence 543 – 545. Revise the last sentence to read "We recommend that the data be periodically evaluated to identify possible trends or drifts in the process and corrective action or follow-up actions be implemented as needed."	This is too prescriptive. Tracking operator errors to measure training effectiveness goes beyond the product itself. Training effectiveness should be measured in basic GMP compliance programs not product validation protocols. In addition, FDA recommendations of meetings and attendees are too prescriptive.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	543-545 (Stage 3- CPV)	Text on operator errors	Delete	Text seems out of place in Process Validation guidance
F	543-548 (Stage 3- CPV)	Production line operators and quality unit staff should be encouraged…..	Recommend removal of this section of the paragraph.	The intent of the guidance is not to provide direction on personnel training or how to manage production and quality functional areas at a manufacturing site.
A	556-567 (Stage 3- CPV)	Process qualification	Process confirmation	Agreement with the Compliance Policy Guide
F	562-563 (Stage 3- CPV)	The data should be assessed periodically to determine whether re-qualification should be performed and the extent of that requalification.		Unclear if equipment qualification is meant. If yes, propose to delete because the firms quality system should handle that.
F	567 (Concurrent Release)		Add description	It should be clearly stated which Process Validation stage has to be completed at the time of submission/filing and pre-approval inspection
D	567 (Concurrent Release)		CPG refers to batches as conformance batches. This document refers to PQ batches. Consistent terminology should be considered	
D	567-568 (Concurrent Release)	Concurrent Release of Performance Qualification Batches section	Concurrent release needs to be clearly defined in the document.	

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Category	Line No.	Current Text	Proposed Change	Rationale
D	568-569 (Concurrent Release)		Is the requirement to complete the PQ protocol or - in this context - the report?	In most cases, the PQ protocol needs to be completed before the commercial distribution
D	569 (Concurrent Release)	In most cases, the PQ protocol…	In most cases, execution of the PQ protocol…	Clarity. As presently written could be interpreted to mean approval of the unexecuted protocol only.
D	574-579		"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."	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.

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Category	Line No.	Current Text	Proposed Change	Rationale
D	574-579 (Concurrent Release)	Concurrent release might be …used infrequently…	Add that validation of changes justified as low risk to product quality can permit concurrent product release. -------- Revise to include references to continuous processing operations ------- Add CQV … because CQV as one of choices ----- A concurrent release might be considered appropriate if there is a written rational or procedure for this approach. We consider the concurrent release appropriate in the sense of a lean process for release.	Examples for use of concurrent release are too restricted and should be expanded to include situations where risk to product quality is low. ------- This paragraph seems to exclude the possibility for continuous processing which would necessarily require concurrent release. ------- This (concurrent release) should be acceptable when using CQV. ------- FDA expects that concurrent release will be used rarely.
D	574 – 579 (Concurrent Release)		Clarification is needed regarding when FDA is involved with concurrent release activities. Seems to apply to all conditions as written, but I think the intent is for only short supply medically necessary products.	Clarification is needed regarding when FDA is involved with concurrent release activities. Seems to apply to all conditions as written, but I think the intent is for only short supply medically necessary products.

Category	Line No.	Current Text	Proposed Change	Rationale
D	584 – 586		Change sentence to: We recommend that each batch in a concurrent release program also *be evaluated to see if it needs to* undergo stability testing. *If it is, then* this test data *is to* be promptly evaluated to ensure rapid detection and correction of any problems.	Very strongly object to the blanket recommendation to place all lots on stability which are under concurrent release. This decision should be based upon a risk assessment, as some concurrent releases (such as during column resin or filtration membrane life cycle studies) present an exceedingly low risk to product quality.
D	Stability testing 584 - 586	"We recommend that each batch in a concurrent release program also undergo stability testing and that this data be promptly evaluated to ensure rapid detection and correction of any problems."	Stability testing is only included for concurrent validation – guidance for initial PV (PQ per this draft) batches should be included. The need for stability studies should be determined case by case basis for validation batches manufactured as a result of continuous improvement.	Add clarity
D	584 – 586 (Concurrent Release)		The number of batches required for stability should be based on stability requirements, not PQ protocol requirements.	Not all PQ batches released in a concurrent protocol need to be placed on stability. If the firm has a large number of PQ batches scheduled, this may be an unnecessary burden to the stability program.

Category	Line No.	Current Text	Proposed Change	Rationale
D	584-586		"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."	It is recommended to qualify the expectation all batches in a concurrent release program are to be placed on stability.
D	584-586 (Concurrent Release)	We recommend that each batch in a concurrent release program also undergo stability testing and that this test data be promptly evaluated to ensure rapid detection and correction of any problems.	We recommend that each batch in a concurrent release program also undergo stability testing under accelerated and reduced long term conditions and that this test data be promptly evaluated to ensure rapid detection and correction of any problems.	Stability data under at least accelerated conditions would help to identify any major stability issue before it shows up under long term conditions. Long term storage only serves a confirmation of what is already been known and can then be reduced in frequency and to only stability indicating criteria.

Category	Line No.	Current Text	Proposed Change	Rationale
D	584 (Concurrent Release)	Each batch in a concurrent release… undergoes stability…	Distinguish APIs (from DP) Delete sentence, stability is outside scope of this guide. -------- Delete sentence	Each concurrent batch undergoes a stability testing - for APIs this can be very expensive. Stability is a separate issue, especially for APIs where stability data on a process may be collected before PV. ------- There is no scientific basis that warrants the need for stability evaluation to justify concurrent release
A	591-596			It is recommended to acknowledge the requirements in this section refer to knowledge management as discussed in ICH Q10.
C	598-599		Need to clarify that the cGMP compliant part refers to large scale operations	In biotech, most of the data in the PQ stage comes from small scale studies. These are not run in cGMP compliant fashion.
C	601-602		Need clarification on impurity clearance	Companies use different approaches to establish impurity clearance. Also, there is a variety of impurities present. It is not clear what this reference means.

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Category	Line No.	Current Text	Proposed Change	Rationale
F	605	"CGMP documents for commercial manufacturing,,,are key outputs of stage 1, process design"	"CGMP documents for commercial manufacturing…are key outputs of stage 1 (process design) and stage 2 (part a – facility design and utilities/equipment qualification)	Batch records are not written/approved until after facility design and utility/equipment qualification
F	607	We recommend that firms diagram the process flow for the full-scale process.	We recommend that firms prepare approved flow diagrams representing the full-scale production process	Clarity
F	607		It is recommended that the individual firm decide what is best to capture the elements of process design. Process flow diagrams and preservation of these PFD's should not be included in the guidance.	
F	607-608	Process flow diagrams	Delete	Depending on the batch record system process flow diagrams are not reasonable and do not add value for the operators.
F	611		Delete: "of the various scales"	May not have flow diagrams at various scales
A	615 (Analytical Methodology)		Chapter VII. should be placed after 566	This chapter is lost at the end of the document

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Category	Line No.	Current Text	Proposed Change	Rationale
A	617 (Analytical Methodology)		Suggest to adding: '*One part of* process knowledge…'	Inconsistent with the principle to 'build in quality' (line 85)
A	622 (Analytical Methodology)		Statement such as "…methods should be scientifically sound (e.g. specific, sensitive, accurate and have acceptable precision).	(In Analytical Methodology) there should be a statement added about precision. Without acceptable precision, in-process test results are statistically meaningless.
A	626 (Analytical Methodology)	"… particularly stage 2 and 3 studies…" What's this? Should it be Phase 2 and Phase 3 studies?		Clarification required.
A	626 (Analytical Methodology)	Analytical method supporting clinical supply production,	Please explain whether clinical supply production means the production of clinical trial drugs.	For clarification purpose only
A	626	"Analytical methods supporting clinical supply production, particularly stage 2 and 3 studies…"	The wording should be revised to "phase 2 and 3 studies"	Stage 2 and stage 3 are earlier described as components of the validation lifecycle approach (lines 99-106) Phase 2 & refer to the phase of clinical studies.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	626-627		Please clarify process validation requirements for Phase 1-3 or delete method validation requirements for Phase 1-3 (preferred, since this information is redundant to "Guidance for Industry: CGMP for Phase 1 Investigational Drugs", dated July 2008)	While no reference and/or recommendations are made for process validation requirements during phase 1 – 3 clinical studies, such a reference is made for analytical methods.
A	626-627 (Analytical Methodology)	Analytical method supporting clinical supply production, particularly stage 2 and 3 studies, must follow appropriate cGMPs in 210 and 211	It is apparently indicated in the text that cGMP- compliant procedures must be followed for stage 2 and stage 3. Please clarify why this sentence is inserted in the text.	For clarification purpose only
A	626-627		"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."	It is recommended to revise the verbiage in this section to clarify when validated methods are required.
A	650 (References)		Add ICH Q8 (R)---Annex	ICH Q8(R)-(step 3) - Annex on Pharm. Development is not in references. Expected to be approved shortly so could be in final FDA guidance.
A	650 (References)		Q8~~A~~	Reference correctly

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Category	Line No.	Current Text	Proposed Change	Rationale
A	650 (References)		add reference to ICH Q8(R1)	New approved ICH document
A	653 (References)		Q9~~A~~	Reference correctly
		GENERAL COMMENTS		
E	General		Scope needs to be clarified Criteria similar to current ICH Q7a should be added	Cleaning Validation requirements not included Absolutely no reference is made to cleaning validations. Is there a reason to keep this separate from process validation? The document covers facility, utility and equipment and I hoped that it covered cleaning as well.
E	Section I.		Add to this section: 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.	Guideline should only be applicable for new manufacturing process. For established marketed API and drug product there is no need to start new validation activities as result of this guidance. The process verification as requested in stage 3 may be achieved by Product Quality Review and Production Reports.

Category	Line No.	Current Text	Proposed Change	Rationale
E	Scope	The phase discussing "Process Design" needs to mention something about 'Cleaning" Validation/Verification. This is part of the process but is handled as a totally separate item.		
F		Section 2(a) Needs to mention something about direct v. indirect impact or contact with the product.		
B		Section 3 "Stage 3" makes it sound like statistics needs to be updated and run after every batch. If this is the case then there needs to be a time when it can be backed off (at least somewhat)		
E	Scope	No mention of cleaning or changeover performance. Helpful to include a statement at the end of Stage 1.		Cleaning validation and changeover validation or also elements of the process validation strategy.
E		Not covered	Include a discussion on matrix / bracketing approach to process validation	Bracketing is widely used and some guidelines on the use of matrix/bracketing in the context of the new approach would be beneficial

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Category	Line No.	Current Text	Proposed Change	Rationale
E		Not covered	Include a discussion on application of this document to legacy processes being reviewed	Need guidance on application of design elements for existing processes inclusive of ability to apply concurrent release
E			General Comment: The document doesn't elaborate enough on how to address processes that were successfully validated according to previous agency guidance and have no history of performance issues.	Elaboration is needed on how to apply the guidance to already validated processes in order to avoid unnecessary additional work on proven processes.
B			Further clarifications regarding risk assessment would be helpful.	
A			The document shows different levels of innovation, some parts being completely aligned to recent FDA/ICH documents and some parts linked to a traditional approach.	

Category	Line No.	Current Text	Proposed Change	Rationale
F		Facility, utilities and equipment are discussed throughout different portions of the document.	The document is mixing equipment and facility qualification requirements with process validation and in general appears to be stating that there is an expectation that for every product, a separate parallel facility and equipment qualification plan and report must be written. This isn't practical or value added and creates documentation redundancy. Recommend to have one general introduction on qualification principles and reference other guidance.	The intent of the guidance should not be to provide direction on how to qualify or maintain a facility or equipment.
A			Guidance could use a glossary to clarify the meaning of terms used throughout it: e.g. design stage, product-development stage, process-design stage, continued process verification, and process qualification.	

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Category	Line No.	Current Text	Proposed Change	Rationale
A	General Comments		Please 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) - Design Space and relationship to Process Validation principles and practice	Would be helpful to have specific definitions to clarify agency position.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	General Comments		Align with ICH Q7A 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	To maximize the impact of this effort to update the approach to validation on a global scale, enhanced referencing of other guidance documents is beneficial for alignment

Category	Line No.	Current Text	Proposed Change	Rationale
E	General			This guideline will facilitate the full realization and benefits from ICH Q8, Q9 and Q10, 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. There should be guidance and provision for these types of products. In order to bridge the different expectations between this guidance and the earlier version, a risk-based approach may need to be applied.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	General		Qualification - The act of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and comply with specified requirements. Validation - Documented objective evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.	The guidance uses "Qualification" and "Validation" interchangeably (example: line 132). There is already industry confusion on the difference. It is recommended to select one of these terms and use it throughout the guidance. Suggested definitions are provided to clarify these two concepts.
B	General		"The number of samples should be adequate to provide sufficient statistical confidence, where appropriate."	In several sections of the guidance (e.g., lines 427- 432) there is a reference to statistical sampling. It should be noted not all samples taken can be statistically justified, such as ID testing. Please change to add "where appropriate", and suggest a justification of the sampling plan.
----	General comment			In general a very good guidance however we have some specific comments to the wording.

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Category	Line No.	Current Text	Proposed Change	Rationale
A	General	Include a definitions section to define terms		
A	Throughout the document		PQ = Performance Qualification? PQ = Process Qualification? See comment for line 102	To be consistent in terminology
A	Throughout the document		To use risk based approached when making a sampling plan	