SCORECARD: PhRMA Comments on:
Draft FDA Guidance "Drug Product CMC Information" (Docket No. 02D-0526, CDER 1997127)
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Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
MINOR					
I.	43	Organization of an ANDA (2/99)	This Guidance should replace FDA's Guidance entitled Organization of an ANDA (Feb. 1999).	The introduction states that the guidance addresses the content of original ANDAs. Therefore, this guidance should supersede the 1999 guidance on the same topic.	
	68-70		In some cases, the majority of information to address the drug substance or drug product section will be incorporated by reference from a DMF. However an applicant should still provide information to address some of the drug substance and drug product subsections.		
. II. Background A. The Common Technical Document – Quality (CTD-Q) Format	70-73	N/A	It would be useful if FDA could formally estimate when the updated drug substance CMC guidance would be published		
II. Background	131		Please clarify that the reference to "placebos" means placebos used as "place-holders" in a calendar pack dosage form, not placebos used in clinical trials. As this guidance is for original NDAs and ANDAs, it should not apply to clinical trial supplies.		
II.B.	161-162		Add clarification to confirm that the statement, and corresponding rationale, for not providing information for a P subsection should immediately follow the relevant section/subsection number.		
II D.	216		PhRMA recommends that information contained in DMFs be organized to follow the same format and content	For consistency. Clarification	

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			guidances that apply to NDAs and ANDAs. Existing DMFs do not need to be reformatted into CTD format. In addition, appropriate sections of the Quality Overall Summary can be cross-referenced in a DMF.		
	236		A brief, one or two-sentence summary describing the dosage form and container closure system is normally sufficient.	The A and B subheadings are misleading in this case because they imply more detail than is actually required.	
	241		Reword Footnote 8 to more clearly state the level of granularity allowed vs. CTD format	Clarification	
P.1	243-245		We suggest that unified terminology should be a potential topic for discussion at ICH level.	We note that the requirement for CDER Data Standards Manual terminology contributes towards regional divergence.	
III.C (P.1)	265 269		Change to: "In some instances, the composition of distinct sub formulations (e.g., cores, coating) of the drug product **may be** listed separately in the composition statement. In these cases, the composition of the immediate release and extended release portions of the drug product **may be** listed separately."	These changes are suggested to provide flexibility for the presentation. In some instances it may be more illustrative to include both sub formulations in the same table. This should be left to the discretion of the applicant in particular if drug substance is not portioned between the parts of the sub formulation.	
P.1	283-285		Concern has been expressed regarding the need to include tracer compound information in P.1 and P.3. We would propose that tracer information be discussed in P.2, but not included in P.1 and P.3 to allow for consistency between EU and US filings and insure information		

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			is not disclosed.		
	291-293		Separate tables of qualitative and quantitative composition of mixtures should be optional. The applicant may choose to include the information in the standard composition tables.		
	304 (Footnote 10)		Efforts to accept compendia in addition to USP/NF (for example, EP or JP) should be accelerated to provide global consistency.	Global consistency	
	302		Define more clearly what "official compendium" is, perhaps by example	Clarification	
	304-315		Reference to Quality standard should be optional in P.1 since it is required in P.4.		
	307-309		Generally, the applicant's code should not be listed.		
	319-322		We presume that for a proprietary mixture it would be sufficient to state the mixture's function and not to list the function of each component of the mixture, as might be inferred. We seek confirmation of this point.		
III.C. .Amount	332-335		Cross-references are given to either the CTD section number, or the FDA guidance hierarchy. This makes it confusing and difficult to navigate the guidance. One style should be chosen. Example (lines 332-335): "For excipients (e.g., coatings, lubricants) where a range has been justified (see section IV.A.2), the target amount should be listed in composition statement. However, the target and range should be included in the batch formula (P.3.2)." In this case section IV.A.2 correlates with P.2.1.2, and alternately P.3.2 correlates to		

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			section V.B.		
III.B.	326		Revise as follows: "The target amount of each component by definite weight or other measure should be provided on a per unit basis. For liquid products (e.g. injection products, oral solutions), the amount of each component should be expressed in weight per unit volume ~~should be~~ on ~~the~~ a per milliliter basis ..."	This is for clarification and is consistent with current FDA expectation.	
	334		Revise as follows: "... the target amount should be listed in the composition statement."	Typographical.	
	358		Table 1 Example Target Composition Statement We suggest that parenthetical text (such as % composition, which is a Canadian expectation) be added to the table format.	Applicants may choose to add additional columns for example, % composition for consistency with Canadian expectations. In addition separate tables may be provided for each formulation.	
III. Description and Composition of the Drug (p.1) C.Composition Statement	358-359	N/A	Please clarify that, if an official compendium other than USP or NF is also referenced in the NDA/ANDA, such as EP or JP, in order to have a harmonized, global drug product, drug substance, and/or excipients, changes to the specifications and/or test methods in the other compendia can also be handled via an annual report.	There is the possibility that the EP or JP change could require a prior approval or CBE submission in the US if these additional specifications and test methods are included in the NDA.	
III.C (P.1) V.B.(P.3.2)	358 AND 769	USP 26 (P.944)	Replace "Hydroxypropyl Methylcellulose" with "Hypromellose."	To comply with revised official USP 26 name.	
IVA.1.a (P.2.1)	394		Revise to read as follows: "For example, if particle size is expected	BCS can be used to justify omission of this testing.	

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			to influence the bioavailability dissolution rate [note: consider including a statement regarding Dose Volume term > 250 ml (BCS Category 2 and 4)], drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution"		
IV.A.2	427		We suggest that, for clarity, the term "functional excipient" should be defined in the Glossary. See glossary comments for proposed definition.		
	437-445		Eliminate reference of US- recognized ICH countries EU/JP	Consideration should be given to accepting the use of information on "food – grade" materials, when they are used in the US for the first time in an oral human drug product, to limit the scope of the filing package rather than being compelled to treat them in a similar way to a drug substance. The same point also applies to Noncompendial-Non-novel Excipients.	
IV.A.2 Excipients (P.2.1.2)	439-457	N/A	We assume that full CMC information is not necessary for flavors or food additives, which are not compendial.	Clarification	
IV.A.2 (P.2.1.2)	447-457	N/A	Noncompendial-Non-Novel Excipients Define 'non-novel', e.g., used in EU, listed in Inactive Ingredient Guide. We assert that it should be appropriate to consider accepting agents defined in a pharmacopoeia other than the U.S.P. as having adequate data packages to support reduced information in the filing.	Definition needed for clarity	

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	468		Eliminate the word "any". It implies that non-novel excipients are also included in the scope, which may be an unnecessary burden for applicants.		
	489		A brief summary describing the rationale for the development of the drug product should be provided. Add a footnote that the intention is not to require a full development summary.	The P.2.2. section is not intended to provide a comprehensive 'development history' of all work done during development, only the rationale for the development of the dosage products proposed in the application.	
	490-493		Revise as follows: "For modified ... a ~~detailed~~ description of the release mechanism. For novel delivery systems a development summary of the new mechanism should be included"		
IV.B.1	495-499		Revise as follows: "The differences between clinical formulations **used in pivotal studies** and the proposed commercial formulation described in P.1 (i.e., composition statement) should be discussed. "Any **significant** changes between the proposed commercial formulation and those formulations used in **clinical efficacy, bioequivalence** and primary stability batches **(i.e. pivotal batches)** should be clearly described and the rationale for the changes provided."	We recommend adding "<u>used in pivotal studies</u>" after clinical formulations and clinical batches since data from early clinical studies may not be applicable.	
	503-505		Modify sentence two as follows: "**Where appropriate**, a summary of the		

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			development of an in vitro/in vivo correlation..."		
IV.B.1 (P.2.2.1)	511-512	MAPP 5223.2 http://www.fda.gov/CDER/mapp/5223-2.pdf	Appropriate data to support scoring should be included in the submission.		
	529-539 -and- 341-342		Overages should be listed only in the batch formula, not in the composition statement.	Distinction should be made between "overage" to compensate for manufacturing losses, "overage" to compensate for degradation, and "overfill" to ensure proper dose delivery. Inclusion of associated definitions in the glossary would be useful. Manufacturing overages are utilized to achieve the target amount reflected in the composition statement and label, and therefore should not be reflected in the composition statement. It is unclear how, and for what reason, an overfill would be reflected in the composition statement. We suggest removing the example of "ensure proper dose delivery" from this section.	
IV.C. (P.2.3)	580-588		In many (or most) cases, a qualitative description should be sufficient to describe significant differences in the manufacturing equipment rather than a table. The focus should be on critical operating principles or design (SUPAC classification of equipment). If batches of product used in pivotal clinical studies are bioequivalent to commercial scale batches then there should be no need to	This section is an example of information considered excessive for conventional dosage forms.	

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			provide information concerning equipment used to produce "clinical" batches of drug product.		
IV.D.(P.2.4)	589 (entire section) 596		D. Container Closure System (P.2.4) This section could be written more clearly. Perhaps simply reference applicable guidance already in existence. A brief description of the container closure systems listed in P.7 should be provided. Any special storage and transportation container closure systems that may be necessary for proteins or other environmentally sensitive drug products should also be provided.	Clarity	
VI.F.	598		The discussion should consider topics covered in the Guidance for Industry, container closure Systems for Packaging Human Drugs and Biologics (May 1999) that are pertinent to the specific drug product.	Specifics including DEHP labeling requirements are better placed in the guidance Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)	
V.A (P.3.1)	689, 696, 710-713 and footnote 19		CFN and FEI numbers, U.S. agent, and the name and phone number (fax, e-mail etc) of a contact person for PAI are administrative information already provided on the Form 356h. They do not need to be included in CTD section P.3.1 Manufacturer(s). This is not consistent with the spirit of global harmonization.		
V.A.(P.3.1)	692		It is not clear why building numbers are being requested.		
	704-706		Clarification for this bullet is needed to emphasize that only laboratories intended to perform testing on commercial material be listed.		
V.A. Manufacturer	710-713		We strongly suggest that these lines be	This is not relevant to the scientific	

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(P.3.1)			removed: "~~do not agree with the statement, "Facilities should be ready for inspection when the application is submitted to FDA". For all NDA's and BLA's the applicant indicates when the facilities will be ready for inspection on the 356h. It is our understanding that readiness at time of filing is an unnecessary burden on the applicant. If there is a desire to codify the date of inspection readiness, we are willing to discuss having facilities inspection ready 45 days after filing for applications subject to standard review cycles to coincide with the 45 day meeting. This is reasonable since it is highly unusual for FDA to request preapproval inspections prior to the decision to file an application. We would agree that sites should be ready at filing for manufacturing supplements and priority applications.~~"	content of the application. May need to be reconsidered with FDA quality initiative.	
	719, 750-761, Table 2		Reference to quality standards is already required in P.4. It should be optional in P.3.2 Batch Formula.	If the quality standards are provided, With regard to continuity within the application and the applicant's control processes, this information may be necessary. Optional reference to quality standards is particularly important because it reduces the requirements for customization for individual regions.	
	720		Replace "intended validation batch sizes" with "intended commercial batch sizes".	For processes with multiple unit operations that are subsequently combined, i.e., combination of multiple granulations by subsequent blending or combination of coating pan	

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				operations, the validation scale may not necessarily be the same as the intended commercial scale.	
V. Manufacture (P.3) A. Manufacturer(s) (P.3.1) B. Batch Formula (P.3.2) Reference to Quality Standards	759-761	N/A	Remove the word "actual". We suggest that reference to quality standards in 3.2 be made optional as it is referenced in S4.1 We understand that FDA is not expecting to see company documents in this section. Summarization of standards, however, would be consistent with what is currently provided to the European agencies.	"Actual specification" is open to interpretation	
	782-796		The flow diagram and description of the manufacturing process should not include steps that are considered to be general GMP requirements, i.e., weighing of materials.		
V.C.	784		Revise as follows: "A flow diagram should be provided giving the steps of the process and illustrating the movement of components into and the movement of product out of the manufacturing process ~~and showing where materials enter the process. The entire manufacturing porocesss should be depicted (e.g. weighing ...)~~"	Clarifies what should be included in the flow diagram.	
	787		Revise as follows: "The section of the flow diagram which details the actual manufacturing or compounding should ..."	Clarifies in what section of the diagram this information should be included.	
	790		We propose that FDA consider the following concerning critical *steps*.		

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			Critical *steps* (an ICH term) are defined by the development activities. For critical steps an operating range and outcome has been demonstrated outside which a batch cannot continue. A step is NOT critical if it can be adjusted, and/or stopped for adjustment, based on the results of in-process testing without any implication on the quality of the part processed material or finished product. A critical step is not associated with a business/producer risk;. ~~Critical steps in manufacturing processes are typically rare~~; they are company defined.		
V.C.1	790-796		A more precise definition of a noncontinuous process is needed. In-process material that is held must be validated for a time period in excess of the designated "hold time" in the appropriate container/closure system.		
	796		Type of equipment used should be replaced with operating principles and design as defined in SUPAC Equipment		
	809		Eliminate need to provide working capacity of equipment.	We do not believe there are situations when working capacity would be relevant.	
	824		Add the following sentence at the beginning of the paragraph: "If ruminant-derived materials are used or manipulated in the same manufacturing equipment as the new drug product, a statement should be provided regarding control measures (such as sourcing, manufacturing processing conditions, and the nature of the tissues) used to minimize the risk of TSE."	Provides for explanation of exceptions.	

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	832-882		The guidance attempts to establish the policy that all in-process tests are critical in-process tests. We strongly disagree that all in-process tests are critical in-process tests. We propose that the policy discussion proceed in an appropriate forum in order not to interfere with the timeline for completion of the document defining the content and format of the CTD. This definition cannot be incorporated as a requirement until it has been suitably addressed.	Defining all in-process material tests as critical process controls and leading to an accept/reject decision is too restrictive. Some in-process material tests may be used to make manufacturing process adjustments, not to make a decision to accept or reject the material or drug product. For example, an in-process LOD test may be performed for the manufacture of a drug substance, and the next step is determined on the LOD test result. Inclusion of all process controls (line 850, 867) is excessive and unnecessary.	
	843		We recommend including examples of process tests.	To help distinguish process tests from in-process tests.	
	849-852		Revise to read as follows: "Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All critical process controls should be included in the description of the manufacturing process (MPR or narrative)."	"All process controls" are considered too inclusive. Frequently, there are processing controls that have no effect on the quality attributes of the product. These controls may be in place to monitor process yields or efficiencies. These may be added or deleted during routine production and should not require regulatory action to change.	
	852		Add the following after the period: "Process steps and associated controls specified in the narrative that may have a major or moderate impact on the quality of the product are classified as critical. Other process steps and controls specified in the narrative are deemed to have minor	Provides clarification to industry on definition of critical vs. non-critical parameters and gives guidance on approaches to evaluate change at time of authoring original submission.	

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			or no impact to product quality. Changes to process control parameters would be submitted according to the Changes to an Approved NDA or ANDA (November 1999) or Comparability Protocols (February 2003) guidances."		
	867-875		Revise to read as follows: "All critical process controls and critical in-process material tests (as defined above) should be specifically identified in the flow diagram and in the description of the manufacturing process in this section of the application (P.3.3) and in P.3.4. A summary of where information on drug product quality controls should be located in applications submitted in CTD-Q format is provided in Figure 1."		
V.C.3	887-912		Although narrative definitions are given for reprocessing and reworking, the glossary should contain definitions of these terms.	Clarity	
V.D (P.3.4)	920-930		We suggest adding a provision here for applicants to include justification for providing interim acceptance criteria for in process controls.		
	927		Remove the parenthetical material beginning at the end of this line.	Relevant batches to establish critical process controls values do not ordinarily equate to all batch analyses listed in 5.4, only a limited pool from P 5.4 would be used to establish critical process control values.	
V.D (P.3.4)	947-950	II.F.3	The new guidance states: 'when the same analytical procedure is used for both the	A specification limit depends on the precision associated with the	

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			in-process and the finished product test, the acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the finished product specification' We recommend that the section be re-worded as follows: ''when the same analytical procedure is used for both the in-process and the finished product test, the in-process test should be held to a tighter standard in the sense that the probability of acceptance of the finished product test is at least as great as that for the in-process test for true levels of the measured characteristic that bear on the quality of the product.'	reported test result. With some analytical procedures, the precision will depend on sample size or number of samples used to obtain the reportable result. In many cases, we suspect that the sample sizes will not be the same for the in process and finished product test and therefore it is inappropriate to state that the in-process limit should always be tighter without some qualification. We feel the word 'criterion' needs to be better explained.	
	949		The acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the finished product specification or a justification for why it isn't should be provided.		
E. Process Validation and or Evaluation (P.3.5)	956-963		The sentence "Submission of other manufacturing process validation information in the application is not necessary for most drug products" should begin this paragraph, rather than initiating the paragraph with details on critical steps and tests. Please provide examples of where validation documentation other than sterilization validation is necessary for submission, as this information is not typically submitted.	The paragraph currently starts out implying that process validation should be provided, but then later states that this is only required for specific situations. When starting to read the paragraph in its current form, it can be initially misleading.	

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VI (P.4)	981-986	USP 26 General Notices: Tests, and Assays – Procedures (p. 7) USP 26 <1078> Good Manufacturing Practices – Inspection and Testing – Raw Material testing (p. 2327) 21 CFR 211.84 (d)(2) ORA Compliance Policy Guide Chapter 4 (CPG 7132.05 Section 420.400) http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg420-400.html	Revise as follows: "Compendial–Non-novel Excipients: When a compendial excipient is tested according to the monograph standard with no additional testing ~~and the applicant intends to perform full testing on each batch received,~~ the excipient (e.g., Sodium Chloride, USP) can be tested under P.4 with no detailed information provided in P.4.1 through P.4.4."	This section implies that if the applicant does not perform full testing on each batch of compendial excipient received, then detailed information must be provided in sections P.4.1 through P.4.4. PhRMA does not believe it is necessary to supply information on Specifications (P.4.1), Procedures (P.4.2), Validation of Procedures (P.4.3) or Justification of Specifications (P.4.4) for a compendial excipient simply because the manufacturer may accept some of the vendor's results via COA. It also implies that a sponsor cannot utilize vendor qualification in order to accept via COA without providing additional detailed information in sections P.4.1 through P.4.4 of the filing. This is in conflict with the General Notices in the USP 26, which state that application of every analytical procedure is not required for assuring that the batch meets the compendial requirements. Additionally, 21 CFR 211 Subpart E also allows the sponsor the ability to accept via COA, provided qualification has occurred. It is unreasonable to require the pharmaceutical manufacturer to commit to fully test every excipient lot at this point	VI (P.4)

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				in the filing. The testing program is covered appropriately by the manufacturer's GMP program. "Qualified Supplier" and other programs are entirely consistent with regulations and not the subject of the NDA.	
	986-987, 989-990		The following statement needs clarification: "The P 4.1. to P 4.4 information for each individual excipient should be grouped together in the application." It is unclear whether to list P 4.1 to P 4.4 for each excipient separately, or to group each excipient into a single P 4.1 to P 4.4. The applicant should be able to use either alternative. It certainly should not be mandatory to create separate P.4.1 – P.4.4 sections for each excipient, particularly compendial excipients.		
VI. Control of Excipients (P.4)	993-994		It should read "IV.A.2" instead of "IV.B.2"	Incorrect section is referred	
	1003		Please clarify why the "patch" would be different from the drug product.		
VI.A(P.4.1)	1008-1009		The statement that "the excipient can be listed under P.4 with no detailed information provided in P.4.1 through P.4.4" on lines 983-984 conflicts with the statement on lines 1008 - 1009 that "a specification for each excipient used in the manufacture of the drug product should be provided, regardless of whether or not the excipient appears in the finished drug product."	Clarity	
VI.A(P.4.1)	1022-1024, and	21 CFR 211.84	Delete the requirement to identify the	It isn't always known at the time of submission which tests the	VI.A(P.4.1)

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	footnote 27	(d)(1) & (d)(2) and (e) 21 CFR 211.160 (b)(1)	tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's certificate of analysis (COA).	manufacturer will eventually accept on vendor COA versus those which will be performed routinely by the manufacturer. At the time of submission of an NDA, the drug product manufacturer may have only limited experience with some of the excipients. This is especially true when new excipients or new suppliers of excipients are used by the drug product manufacturer, and thus having only a limited history of reliability. The implementation of a reduced testing program by the drug product manufacturer would likely occur well after submission of the NDA. Reliability of vendor testing is a GMP issue, and the information being requested is more appropriately handled under established GMP programs. 21 CFR 211.84(d)(2) states that "a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate validation of the supplier's test results at appropriate intervals."	

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				As long as the standard the excipient will meet is submitted (e.g. NF, USP), the delineation of who does what specific test is unnecessary. It is the responsibility of the applicant, as required by cGMP's, to verify the acceptability of the vendor testing, and to determine what tests they may choose to conduct in-house. As the current PAC Q&A guideline requires that a prior approval sNDA be submitted in order to "delete testing", the result of this submission requirement would be many unnecessary submissions not consistent with a risk-based approach.	
	1027-1030		This example should be deleted.	Other factors contributed to this tragedy.	
VI.A(P.4.1)	1032-1035		Delete the clause "... full monograph testing will be performed on each batch of excipient."	This is a significant concern. Reduced testing and accepting material on a vendor's COA is an accepted practice consistent with cGMPs.	
A. Specifications (P.4.1)	1034 1035-1038		The word "identical" should be changed to "equivalent".	The word "identical" is too restrictive and can be interpreted as any word (or even possibly format) that may be different may not be considered "identical". However, bigger issue is ... simple reference to the USP is sufficient when an applicant may utilize a modified testing protocol, which is equivalent to the USP, but not	

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				identical. [It's not clear what this sentence means of the reasons for the " . . ." Needs to be re-written for clarity] For example, modifications to provide a harmonized test scheme, which ensures full compliance with two or more compendia (EP/USP/JP). This provides an acceptable risk approach for the pharmaceutical industry and minimizes numerous and burdensome submissions to product applications. One excipient may be utilized in many products owned by the applicant, and minor and insignificant changes to a testing scheme for one excipient could trigger numerous modifications to applications, creating a non-value added activity for both the applicant and the FDA.	
	Footnote 27		Move " [27] " to the end of the following sentence, i.e., "At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1)) [27]." Add the clause "For the tests accepted by the manufacturer on Vendor COA" to the beginning of Footnote 27 preceding "The drug product manufacturer must establish the reliability..." Delete "However, the specification should indicate the tests that will be performed once the reliability of	Clarification	

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			the supplier's results has been established..."		
	1038-1041		We request a definition of the term "official compendia monograph." We would propose some latitude be provided going beyond USP/NF to cite other recognized compendia such as EP and JP [spell out at least once the meaning of EP and JP]. Otherwise, if the material is Ph Eur, we would need to ensure that it meets NF or another official compendium. We question the value added for the extra testing that it will represent.		
VI.A (P.4.1)	1038-1041 1038 – 1041 Footnotes 10, 21 and 26	USP 26 & NF 21 General Notices: "Official and "Official Articles" Sections 201 [321] (j), and 501 [351] (b) of the FD&C Act	"If the specification for an excipient is based on a compendium other than an official compendium, the excipient should still conform to the monograph in an official compendium if there is such a monograph." The following terms, from the above statement, are confusing and need clarification, 'official compendium', and 'conform to the monograph.'	What compendia are not official as it relates to this document? Reference is made, in Footnote 10 (p. 8), in Footnote 21 (p. 20) and again in Footnote 26 (p. 27) of the Draft Guidance to the official compendium as defined in the Federal Food, Drug, and Cosmetic Act. Perhaps the Footnotes could simply state the titles for the two official compendia: USP-NF and Homeopathic Pharmacopoeia. It would be helpful if Lines 1038-1041 of the Draft Guidance stated more clearly the specific status of the Ph. Eur., BP, and JP-JPE.[spell out these terms at least once] This is important for a few excipients that have monographs in one of these other compendia, but not in the USP-NF. Conforming to the "monograph"	

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				has a different meaning than conforming to the "compendia", e.g., meeting compendia means complying with the General Notices, applicable General Chapters and applicable GMPs as well as meeting the requirements of the monograph. Also, the legally recognized "official compendia" for the FDA are the USP-NF and the Homeopathic Pharmacopoeia as per the Federal Food, Drug, and Cosmetic Act.	
	1044		Replace "EP" with "Ph.Eur."	Use official abbreviation	
	1046		Replace "result obtained from USP", with "decision will be based on science. If USP is not used, an explanation should be provided as to why USP is not appropriate."	Should be verification as to currentness of USP. Additionally, product specific quality may require use of the "non-USP' grade of material if it is more suitable.	
VI.B.(P.4.2)	1053 1063-1064		We request examples of other FDA recognized standard references. If a "list" exists, we suggest adding a reference here to this list.		
P.4.2.B.	1055	AOAC International Book of Methods APHA Standards	The document cites the AOAC International Book of Methods as a FDA-recognized standard reference. Microbiological methods may be also found in APhA Standards, e.g., Standard Methods for the Examination of Water and Wastewater and Standard Methods for the Examination of Dairy Products and ASTM standards, i.e., Bacteriological challenge of sterilizing filters.	Acceptable alternate microbiological methods may be used.	

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VI.C. (P.4.3)	1062		Revise to read as follows: "Analytical procedures for excipients should be validated or verified as appropriate.	We do not believe that "all" analytical procedures need to be validated or verified and that this should be required only "as appropriate." For example, compendial methods are well characterized and thus need not be validated.	
VI.C (P.4.3), and VII.C (P.5.3)	1066 – 1072, and 1273 – 1274	USP <1225> Validation of Compendial Methods 21 CFR 211.194 (a)(2)	Clarify the statement to exclude the requirement of submitting validation for compendial excipients. For example, replace the following statement: "Validation information should be submitted if there are special circumstances. For example, submission of validation information for an excipient can be appropriate if a characteristic of the excipient or the excipient itself is critical to product quality (e.g., adjunct, carrier) but the critical nature of the excipient cannot be or is not assessed as part of the drug product testing" with the following: "Validation information should be submitted for additional test(s) required by special circumstance for test(s) that are not covered in or performed as described in an official compendium. For example, additional testing beyond the monograph requirements may be needed if a characteristic of the excipient or the excipient itself is critical to product quality (e.g., adjunct, carrier) but the critical nature of the excipient cannot be	Per USP 26 <1225> "...users of analytical methods described in the USP and the NF are not required to validate accuracy and reliability of these methods, but merely verify their suitability under actual conditions of use." Per 21 CFR 211.194 "(If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice)"	

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			or is not assessed as part of the drug product testing." Revise the statement "Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product should be provided" to read "Analytical validation information for non-compendial methods, including. . .should be provided."		
	1079-1081		Add at the end of the sentence the following: "if additional testing is performed because it is critical to the product performance or manufacturing process".	Clarification	
	1081-1082		The justification of specifications for non-compendial excipients as recommended for drug substance should not typically be required for most non-compendial excipients. It is more appropriate for novel excipients.	Clarification	
VI.D (P.4.4)	1089 – 1094	21 CFR 211.84 (d) (2) ICH Q7A Section 7.31 http://www.ich.org/pdfich/Q7Astep4.pdf	The CoA for the excipient(s) are provided in the Executed production record in the regional section, therefore, there is no reason for the inclusion in P.4.4. Whatever tests the drug product manufacturer performs for the same lot will also be available in the production record, however, this may be limited to ID testing.	The results used to accept the material, regardless of who performed the testing, are available in the executed production record (R.1.P.) As such, we do not support submission of the information in the noted section. The request for both vendor COA results and drug product manufacturers results for	

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				components used in lots provided in the executed batch record(s) is an encroachment into the GMP responsibility of the applicant to establish the reliability of the supplier's analysis. The applicant may choose to perform comparative testing to establish vendor reliability for excipient lots other than those presented in the executed production records and at a time after submission or approval of the application. If it is necessary to determine whether appropriate quality systems are in place for control of vendors, this could be done during inspections.	
VI.D (P.4.4) VI.D (P.5.4) XII.A.2 (R.1.P)	1092 – 1094, 1308 – 1309, and 1819 – 1821	N/A	In the statement, "Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate," change "as appropriate" to "where practical." Delete the next sentence which states: "Use of terms such as conforms or meets specification is discouraged." Use of terms such as "conforms" or "meets specification" should be appropriate to use when it is clear what specification the test result has been assessed against.	It may be difficult to express all results numerically or qualitatively. For example, some identity tests have several acceptance criteria within one identity test. Identity A in the USP monograph for Aluminum Monostearate specifies that when fatty acids are liberated, they float as an oily layer on the surface of the liquid, and the water layer responds to the test for Aluminum. In these cases, the use of the terms "conforms" or "meets specifications" should be acceptable.	
1102	1102-1104		Revise to read as follows:		

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			"Furthermore, for excipients derived from ruminant materials, the application should provide control measures (such as sourcing, manufacturing, processing conditions, and the nature of the tissues) used to minimize the risk of TSE."		
	1117-1126		We propose that compendial references for excipients used by a new route of administration and food use information for oral human drug products may be useful to justify an intermediate type of information package.		
	1121		Please move the entire paragraph starting with "Additionally, full details of manufacture ..." to Sec. IV.A.2 under Novel Excipients.	Paragraph 1121 contains information more appropriate to be referenced in the Pharmaceutical Development Section.	
VII.A. (P.5.1)	Footnote 30 (p.32)	Subject Guidance, Sections VI.A, and VI.B	Change "VI.B" to "VI.A".	The information on interchangeable chapters is provided at the end of section VI.A in the Guideline, not in section VI.B.	
	1147-1149		Although the request to include procedures used only to generate stability data in P.8.3 is consistent with the CTD Q Q&A it presents a potential for confusion because Items P.5.1 and P.5.2 can also be appropriately viewed as the complete statement of all regulatory tests and methods. Section P.8.3 could refer back to P.5.1 and P.5.2. Methods exclusively used during stability testing that are not going to be used in the future appropriately belong in P.8.3.		
	1149		Include definition for "sunset provision."	Clarification	
VII. Control of Drug Product (P.5)	1162 1174		The inclusion of release criteria should be an option not a US requirement.	Release criteria are an internal cGMP issue and not an application	

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	(Table)			issue. The example cited (Assay), while representative of a European application approach, should be considered an optional submission used for purposes of a global submission package and not a U.S. requirement.	
	1173 (footnote)		Section VI.B does not contain the information indicated in footnote 30, page 32 (guidance on USP General Chapters that are interchangeable with EP or JP analytical procedures).	Clarification	
	1174 (Table 3)		We trust that IPCs such as "core weight" was provided for example purposes only, and not as an indicator that tablet weight should be part of product release testing.	Non-functional tests such as dosage unit weight are of limited value as accept/reject criteria; tests such as assay or dissolution provide more useful data. Further, the IPC example again brings up the question if the testing needs to be carried out in the Quality Unit or lab.	
	1174; Table 3		Re: Degradation Products, Unspecified Degradation Product, Individual Unspecified Acceptance Criteria, a reference is needed to indicate that the acceptance criteria is the identification threshold per ICH Q3B-R.		
A. Specifications (P.5.1) Periodic Quality Indicator Tests B. Analytical Procedures (P.5.2)	1176-1231	N/A	It would be useful for FDA to allow EP and JP analytical procedures to be referenced rather than needing to provide	As stated earlier, the issue of change control management needs	

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	1250-1253		a copy of the method.	to be addressed for EP and JP methods that may be referenced in an NDA.	
	1194		Insert "more" before "likely".	Grammar	
	1201		Delete the word "all."	Clarity	
	1214, 1219-1221		Revise to read as follows: "....the PQIT will be performed on each subsequent batch until sufficient data is generated to support PQIT."	The commitments imply a large GMP impact.	
	1254-1257		We propose that microbiology, sterility, bacterial endotoxin tests be exceptions to the requirement to specify which pharmacopoeial method, from the options available for these tests, is being used.	Since it is necessary to validate these methods, and since they may be carried out at contract laboratories we recommend that, for logistical reasons, the filing should specify the "parent" monograph only.	
	1276-1277		We recommend that FDA clarify the meaning of the statement: "This information should be provided for all analytical procedures listed in the specification."	The level of validation required to demonstrate that analytical procedures are suitable for their intended use varies for each procedure type. Certain procedure types other than identification tests, quantitative tests for impurity content, limit tests for the control of impurities and quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product do not require any information. For example, we would not expect to provide validation information for the appearance test in a specification.	

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				We might provide verification information for a compendial method.	
VII.D.(P.5.4)	1288-1291		While Batch analysis data from all requested lots may be provided, we understand that not all of the batches may be used for the establishment of specifications.		
	1292		A COA does not need to be provided here if collated batch analyses data are included.		
	1301		Container closure should not be included in the metadata for batch analysis. It is not relevant.		
	1304-1305		Excipient batch numbers should not be mandatory.	At the discretion of the sponsor, novel excipient batch numbers could be provided.	
VII.D (P.5.4)	1307-1308		Use of terms such as "conforms" or "meets specification" should be appropriate to use when it is clear what specification the test result has been assessed against.		
	1313-1315		The statement that "batch analysis reports should include results from all tests performed on the batch including tests that are not part of the proposed specification" may not be appropriate. For example, batch analysis is not the appropriate place to report the additional testing performed during validation. We suggest that is inappropriate to require results from all tests that are not part of the proposed specification. Perhaps the requirement should be limited to data in support of named tests, considered for inclusion but omitted on the basis of data,	To facilitate paperwork reduction, only data relating to test referenced in application should be provided	

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			e.g. chiral testing. In addition, not all batches in a batch analysis are considered relevant for certain tests.		
	1343-1351		Please clarify the rationale for including drug substance impurities in this section.	If impurities are appropriately characterized in the drug substance section and not drug product degradation products, we do not understand why they would be repeated in this section. A reference to the appropriate Drug Substance sections could be provided instead of listing impurities again. If the purpose is to allow the reviewer to understand/ignore the drug substance impurities that are appropriately controlled the information can be provided in that context.	
	1368		"Active Ingredient" should read "Drug Substance" to provide consistent terminology throughout this guidance document.	Clarity	
VII.E.2 (P.5.5)	1371		Attempts should be made to identify all degradation products found at significant levels (what does significant mean here?) in the drug product. Reference ICH Q3B.	Clarification, harmonization	
VII.E.	1386-1391		Revise as follows: "~~An applicant is aware of the~~ If solvents are used in the manufacture of the drug product, ~~and in most cases those being introduced from other sources (e.g. drug substance, excipients), Because these are known,~~ the identity and presence of residual solvents in the finished drug product should be established and	Residual solvent testing of the drug product should include only those solvents used as part of the drug product manufacturing process. Residual solvents from the API or excipient manufacturing processes should be controlled with specifications established for the API and excipients.	

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			controlled. Solvents introduced from drug substances and excipients should be controlled at the drug substance and expcipient level, not at the drug product level. ~~Can usually be confimed bysuing routine analytical technicques. In some cases, structureal characterization of an unknown impuritiy can determine that the impurity is a residual solvent."~~		
IX. (P.7)	1531		The guidance should mention the container closure system for the proposed marketed drug product.		
	1533		Because it is not defined in the FDA guidance "Container Closure in Systems for Packaging Human Drugs and Biologics", we suggest that "Functional secondary packaging components be defined in the Glossary, and propose the following definition: "Functional secondary packaging: Packaging that ensures the product meets the necessary quality criteria by offering protection against degradation (light) or by enabling appropriate and accurate metering and dosing of the product." We suggest that, for consistency, the agreed definition should also be included.		
	1570		Please clarify the term stability study reports. We believe the term is interchangeable with "results of stability studies" mentioned in line 1569. We do not believe there are any requirements beyond the tabulations of stability data in the stability tables.	Clarification	

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X.C.(P.8.3)	1584-1593		Revise to read as follows: "A summary of any significant changes that would impact the results should be provided..."	This would eliminate the need to report trivial changes.	
	1577		The methods in P.8. are methods that will not be used for stability testing post approval. All release and stability methods for post approval testing should be included in P.5.1 and P.5.2 if these sections are viewed as a complete statement of the regulatory methods.	Clarity	
	1597		We suggest revising this statement as follows: "Based on dosing directions included in the product labeling, compatibility data with. ...should be provided in P2.6"	Clarity	
	1607-1609		Delete sentence on providing stability data to support holding of materials. Although this type of data is necessary, it should be referenced in the appropriate sections justifying the process so as not to confuse it with the formal stability testing of dosage form/packaging addressed in this section.		
	1617-1622		We recommend rearranging this paragraph To the extent stress studies are used to support the items listed in lines 1620-1622, data should be included. If the results of stress studies do not impact these items they need not be included; the first sentence of this paragraph suggested otherwise.		
XI.C. Appendices (A.3)	1762-1763		Change "IV.B.2" to "IV.A.2".	Incorrect section is referenced	

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XIIA.1 (R.1.P)	1793-1795; 1799-1801		Delete "Phase III clinical,". Add the following: "In cases of multiple strengths, one batch per strength is typically sufficient for submission."	The cited CFR requirement for executed production records requires only batches from **bioavailability or bioequivalence studies** and **primary stability studies**. The expansion of the current CFR requirement to representative Phase III clinical batches is inconsistent with current regulation and will add no value to the review process. Information on formulation development is provided in the Pharmaceutical Development Section. We support providing adequate information to thoroughly explain and justify the development of the product, but that information is more appropriately summarized within the application, not in providing additional volumes of batch records.	
XII.B(R.2.P) Comparability Protocols	1826-1830		Please change wording from "A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of postapproval manufacturing changes..." to "...to provide evidence for equivalence for specified..."	From a statistical point of view, one cannot demonstrate (prove) a lack of effect (null hypothesis). A comparability protocol can only give evidence that an effect is within an acceptable range. A comparability protocol is an equivalence test (not a hypothesis test), but cannot demonstrate lack of effect.	
Attachment 1	1921	USP <1111>	The Microbial Limits for specific dosage forms will be specified in USP <1111> Microbiological Attributes of Non-sterile	The absence of specified microorganism requirements would depend on the dosage form	

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			Pharmaceutical Products.		
Attachment 1	2010	USP<61>	Reference to USP<61> acceptance criteria for total aerobic microbial count is not appropriate for transdermal patches.	The microbial limits for transdermal patches are based on the surface area of the patch, not its weight.	
Attachment 1	2061	USP<51>	It is recommended that the document cite USP <51> Antimicrobial Effectiveness Tests for the method for preservative effectiveness.		
Glossary	2117-2256		Consider adding the following list of terms: Critical Process Control Critical Step Critical Tests Functional Excipient: We propose the following definition: A functional excipient is either: 1) An excipient that performs a role in maintaining product quality during shelf life, e.g. an antioxidant, or anti-microbial preservative or 2) An excipient that performs a role in achieving a desired *in vivo* performance, e.g. a release rate controlling excipient Non-compendial Excipient Novel Excipient- add suggested definition Sunset Testing		