FACILITY AUTOMATION MANAGEMENT ENGINEERING SYSTEMS
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Tuesday, September 30, 2003

Documents Management Branch [HFA-305]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance For Industry on Drug Product: Chemistry, Manufacturing, and Controls Information [Docket No. 02D-0526, 68 Federal Register, 4219, January 28,2003]

To Public Docket: 02D-0526:

The additional comments being submitted are designed to address issues raised by other commenters' formal comments that appear to be at odds with the law (**Federal Food, Drug, and Cosmetic Act**, as amended ["**FDC Act**"]) and/or the current good manufacturing practice ("**CGMP**") regulations for drugs (**21 CFR 210** through **21 CFR 226**).

Hopefully, these comments, contained in the pages that follow, will help the Agency to issue guidance that, unlike the present guidance and, in a few instances, the proposed Draft Guidance, fully complies with the **FDA Act**'s requirements for **CGMP** and the requisite adherence thereto that is required of drug product manufacturers with respect to the requirement ***minimums*** set forth in the applicable **CGMP** regulations.

Finally, these comments are designed, where possible, to assist in speeding the overall application review process.

Should the reader have any questions, they should address them to reviewer@dr-king.com,

Respectfully,

This Reviewer

A Review of Formal Comments To Public Docket 02D-0526

Introductory Comments

Having read the comments submitted by other commenters as well as those submitted by F.A.M.E. Systems, this reviewer finds that some seem to have a misunderstanding of the scope of current good manufacturing practice (**CGMP** [also abbreviated by some as "**cGMP**"]) as it applies to drugs and drug products.

These commenters act as if **CGMP** is only an inspectional issue and not an application submission issue.

Time and time, I read some proposed item is a **CGMP** issue that need not be included in the Chemistry, Manufacturing and Controls ("CMC") section of an application (Abbreviated New Drug Application ["ANDA"] and New Drug Application ["NDA"]) because it is a **CGMP** issue that need only be addressed during inspection.

Obviously, these commenters have forgotten **CGMP** is a requirement explicitly incorporated into the United Statutes codified statutes (**Federal Food, Drug, and Cosmetic Act** ["**FDC Act**"], **21 U.S.C. Title 9**).

These same commenters also seem to forget that it is improper for an application evaluator to recommend any application that said reviewer does not know conforms to the requirements of **CGMP** – because to do so could risk that reviewer's recommending an application that produces adulterated drug product.

Further, these commenters seem to overlook the fact that the inspection personnel use the CMC section as the basis for the planning and preparation for as well as the execution of their pre-approval inspection ("PAI") audits.

Given the requirement that each "new drug" application must provide proof that the application complies with all regulatory requirements and the law, including the **CGMP** requirements of the **FDC Act** as well as those legally binding requirement minimums set forth in **21 Code of Federal Regulations ("CFR") 210** and **21 CFR 211** (as well as the requirements set forth in the other applicable sections of **21 CFR Title 9**), the CMC section should be required to provide proof (by statement supported by documented evidence) of compliance with all **CGMP** requirement *minimums* as well as, if it does, those areas where the submitter's systems exceed the requirement *minimums* of the **CGMP** regulations governing drug products and the manufacture, processing, packing, and holding of drug products including the concomitant packaging, labeling, testing and quality control operations (**21 CFR Parts 210** through **226**.).

Finally, were the United States Food and Drug Administration ("**FDA**") to continue to propose guidance that permits proof of less than the **CGMP** *minimums*, the Agency, and those publishing such, would be guilty of subverting the regulatory process and, perhaps, subject to prosecution under the sections appertaining thereto in the **FDC Act**.

Based on a 1988 United States Supreme Court decision, the **FDA** has no discretion to recommend or allow non-compliance with any clearly written regulation.

Moreover, though firms continually point to the **FDA** as the controlling authority over their activities, that Supreme Court decision found that no firm can

validly use the **FDA**'s failure to enforce any clear regulatory requirement as a defense in any legal proceeding where the firm has not complied with any clear regulatory requirement.

Because the **CGMP** regulations set forth clear requirement *minimums*, any firm that submits an application that does not provide proof that their systems comply with all of the requirement *minimums* established therein is knowingly submitting a deficient submission.

Regardless of the guidance issued by the Agency, when it finds that a firm has knowingly submitted a deficient application, the **FDA** should reject that application for cause and only resume their review when the firm has corrected all deficiencies, and submitted a non-deficient application that contains a certification that the application complies with all regulatory requirement *minimums*.

In that regard, this reviewer would suggest that the FDA require, for each new drug and abbreviated new drug application, the top management of the firm to sign, under penalty of law, a certification that the product and processes:

a) Comply with all of the applicable requirement *minimums* set forth in **21 CFR 210** through **21 CFR 226** and

b) Each batch produced from the pivotal batch onward was and, if the application is approved, will be produced in full compliance with the requirement *minimums* of **CGMP**.

Such a requirement would: a) certainly be a strong incentive for firms to comply and b) ease the FDA's prosecution of any instance where the Agency finds non-compliance.

[**Note:** Unless noted, the original comments will be quoted in a condensed font (Perpetua). Similarly, the quotes directly from the draft guidance, the CGMP and other regulations, and the FDC Act will be quoted in a stylized font (Lydian), the quotes from any official compendium will be in a Times New Roman font and this reviewers comments will be in a publishers font (News Gothic MT). These font changes are made to make it easier for the reader to differentiate the source of the various text passages in the review that follows.]

REVIEW AND ASSESSMENT OF INDIVIDUAL COMMENTS

Unless a specific science-based, regulation-based, or other issue (for example, a grammatical, spelling or word order error) is raised concerning a given comment in this review of the formal comments to FDA Docket 02D -0526 that were available electronically to this reviewer as of **9 September 2003**, the commenting firm's or individual's comments are, in general, not opposed by this reviewer.

Also, the review order chosen by this reviewer is descending (based on the comment number ("C-nn") assigned to the commenters by the Agency).

A Review of Formal Comments To Public Docket 02D-0526

PhRMA's Submission Dated July 30, 2003 To Docket 02D-0526: "C-16"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow. When addressing comments made in a tabular format, this reviewer will (to the extent required) preserve the commenters' format and, in general, appropriately place the reviewer's remarks after those of the commenter.]

With respect to the introductory comments, please consider the following.

As the commenters say, "the Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies ... This guidance suggests useful recommendations for providing the **FDA** information to support applications for new drug products. However, we conclude that its usefulness can be enhanced through the suggestions and revisions detailed in the attachment. These comments represent the collective view of the membership of PhRMA. We believe the following general observations emphasize major points where the usefulness of the guidance may be enhanced:"

"1. The concepts of critical steps, critical in process controls and critical tests need clearer definition. Because of the varied use and interpretation of the term "critical" throughout the industry, PhRMA recommends that the FDA solicit industry input and general agreement on the appropriate application of this term through a public workshop before including it in a guidance document."

Contrary to what PhRMA is proposing, the **FDA** does not need to hold a public workshop to define the terms critical steps, critical in-process control and critical test.

This reviewer can easily define the adjective "critical" in a manner that precludes the need to define these specific phrases.

By statute (Federal Food, Drug, and Cosmetic Act as amended [**21 U.S.C. Title 9**]) and by legally binding regulation (**21 CFR 210.1**), ***critical*** means "*required to be controlled in a manner that complies with, or pertaining to any requirement specified in, the drug CGMP as set forth in **21 CFR 210** through **21 CFR 226**.*"

This is the case, because, as **21 CFR 210.1** states (emphasis added):

"(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum currentg ood manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply,s hall be subject to regulatory action"

failure to meet *any* of the *minimums* established adulterates the drug and subjects the person responsible to criminal regulatory action.

Therefore, anything required by **21 CFR Parts 210** through **226** is obviously "***critical***" to those that manufacture drugs.

Any entity that falls outside of the clear requirements set forth in **21 CFR Parts 210** through **226** or any thing that is above the minimums established therein is, therefore, a "**non-critical**" entity.

Hopefully, the correctness of these definitions will be seen by the Agency and they will, as they should, simply incorporate them into the Glossary.

Because tablets are the most prevalent dosage form, this reviewer offers this illustrative example:

- Film coating a tablet is a critical step because its execution may affect the critical properties of the drug product (**21 CFR 211.110**).
- Making certain that the correct color is applied is a critical control because it affects the "identity" of the tablets – they are required to match their description (for example, light blue).
- However, comparing the tablets from different coating pans to determine whether their color shades are close enough together that the pan loads can be mixed or the shades are not and the pan loads need to be kept segregated is a non-critical control.

Moreover, to do as the commenters propose would be a waste of precious Agency resources and needlessly delay the updating of the CMC guidance to meet the **CGMP** *minimums* in all areas – something that the current guidance fails to do.

"2. To demonstrate support of the ICH process, the guidance should be expanded to recognize materials that have compendial designations from non-USA ICH participants. PhRMA recognizes that the Federal Food, Drug and Cosmetic Act only recognizes the USP/NF as official compendia. However, provisions should be made to minimize extra testing that is required in this draft guidance when using excipients that hold ICH participant compendia designation. This will help move our industry towards global consistency and the spirit of harmonization.

This comment is inappropriate, because: **a)** the compendia are in the process of being harmonized; **b)** the **CGMP** requirements clearly spell out what is required; and **c)** doing less than the **CGMP** regulations *minimums* adulterates the drug products so produced (**see Reviewer's response to Commenters' 1**).

Therefore, to be **CGMP** compliant, as required by law, the guidance can recommend doing more but it cannot recommend doing less than the applicable **CGMP** regulations require.

"3. Make allowances to accept vendor Certificates of Analysis (COA) for compendial excipients. Because it is not always known at the time of submission which tests a sponsor will accept on COA, PhRMA does not see the value added by identifying the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's COA."

Based on the comment made here, PhRMA apparently does <u>not</u> see the value of **CGMP** compliance.

The **CGMP** regulations require the manufacturer not only to spell out the tests that they will routinely perform but also establish by documented evidence that said test comply with all applicable **CGMP** regulations.

Technically, the submission must have tests and specifications for components that are sufficiently specific to ensure that each shipment of each lot of each component (including excipients) is the "same" as those for the lots used to produce the batches of drug product being submitted in support of the application.

The preceding is especially important for "solid" formulations where the physical properties (which are typically missing from the official compendia or, when listed, usually too broad to assure that subsequent lots are the "same" as the lots used to produce the batches upon which the submission is based) of the components are critical to ensuring the uniformity of the drug product produced using the components and processes submitted in the application.

In the **CGMP** regulations, the use of a supplier's "Certificate of Analysis," (called "report of analysis" in the CGMP regulations) in lieu of testing is predicated upon:

a) The performance of "**at least one specific identity test**" on lot-shipment representative samples – not a composite thereof – of such component by the manufacturer. [**Note:** In such cases, the submitter would need to develop, establish the validity of, and submit the specific identity testing it proposes to do along with the proofs that establish that said identity testing is truly **i)** lot-shipment representative and **ii)** component specific with respect to all parameters that can adversely affect said component's performance in the formulation being submitted. After all, how can an **FDA** reviewer approve an application unless the testing guarantees that all future batches are the "same" as those used in the pivotal clinical or bioequivalence batch or batches being submitted to support the application?]

b) **"The manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals."**
[**Note:** in such instances, the submitter would need to submit the supporting documentation that demonstrates that the submitter has established the reliability of the supplier's test results ("**validation of the supplier's test results**") and proves that the submitter has established a validation interval that is scientifically appropriate based on comparable data results obtained from more frequent comparisons. In cases where the supplier is a new source, initially representative samples from each shipment of each lot should be tested and compared to the representative sample data obtained by the supplier. In cases where the supplier does not take and test "lot representative samples from each lot, a manufacturer should not attempt this approach. In such cases, the applicant either needs to induce the supplier to: **a)** generate batch-representative test values on each lot the manufacturer purchases and **b)** agree to only ship consecutively ordered containers from the filling of each lot to the manufacturer or not attempt to use the "report of analysis" approach. This is the case for **Condition** "**a)**" BECAUSE there will be no *scientifically sound*

basis for comparing non-lot-representative results obtained by the supplier to the **CGMP**-mandated lot-shipment representative results obtained by the applicant. **Condition "b)"** must be satisfied to ensure that one can use the results obtained to prove that the samples taken are "lot" representative and that the lot is sufficiently uniform. When the drums are certified to be and labeled in sequence, then the material in the bottom of drum "n" should be the same as the material in the top of drum "n+1." When there are gaps in the sequence, each drum must be sampled more intensively (typically, top, middle and bottom at a minimum). Moreover, the testing lab cannot expect the results obtained for the sample from the bottom of container "n" and the values obtained for the sample from the top of container "m" to be the same. {Factually, there instances where an application has been approved but the firm could not reliably manufacture releasable batches because, after approval, the component specifications permitted the use of components whose physical parameters were not the "same" as those used in the submission batches and the suppliers, for whatever reasons, could no longer match the specifications values found for one or more of the components used to make the bio-equivalent batch.}]

Since suppliers' reports of analysis typically do not provide a "report of analysis" that furnishes all of the requisite information required for each component ("**conformity with all appropriate written specifications for purity, strength, and quality**"), **the applicant must commit to performing lot-representative testing on each shipment of each lot for the tests that the supplier does not report.**

For example, most suppliers' "reports of analysis" do not report a *purity* value (as the commenters should know, "assay" is synonymous with the requisite "**strength**" requirement not with "**purity**" and the scientific definition of "**purity**" is well understood for discrete chemical entities).

[**Note:** Most suppliers do not report "**purity**" (best reported on an "as is" minimum weight-percent basis) of the active ingredients. The drug-product manufacturers must know the active ingredients' purity in order to appropriately comply with the "**not less than 100 percent**" requirement set forth in 21 CFR 211.101(a)). Thus, the manufacturers need to generate this value. This is the case because, in general, the official compendia do not provide a scientifically sound test procedure or appropriate specifications for a component's "purity" even though, for the active ingredients and some other "active" components, such values are critical to a generating a valid **CGMP**-compliant formulation).]

Having addressed the commenters' general observations, this reviewer will now examine those presented in the thirty-three pages of tables downloaded from the docket.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

Section	Guidance Line	Comment / Observation	Rationale / Justification
I	43	This guidance should replace FDA's Guidance entitled Organization of an ANDA (Feb. 1999). This reviewer disagrees; this guidance should replace the guidance that the FDA stated in the introduction it was to replace, namely, "*Submitting Documentation for the Manufacture of and Controls for Drug Products* (February 1987)."	The introduction states that the guidance addresses the content of original ANDAs. Therefore, this guidance should supersede the 1999 guidance on the same topic. Contrary to the commenters' remarks, the "Introduction" (Lines 26-33) actually addresses both ANDAs and NDAs, "This guidance provides recommendations on the chemistry, manufacturing, and controls (CMC) information for drug products that should be submitted in original new drug applications (NDAs) and abbreviated new drug applications (ANDAs). The guidance addresses the content of original NDAs and ANDAs. The guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format (see section II.A and B). The recommendations apply to all NDAs and ANDAs, although more detailed guidance on the content of an application may be available in separate guidance documents for specific types of drug products or dosage forms (see section II.C). Based on the preceding facts, this comment should be ignored.
I.	68-70	In some cases, the majority of information to address the drug substance or drug product sections will be incorporated by reference from a drug master file (DMF). However, an applicant should still provide information to address some of the drug substance or drug product subsections. While this reviewer will leave it up to the **FDA** as to whether or not to make the changes proposed, this reviewer thinks that this change would require amending the requirements for Type 2 DMFs to incorporate by reference compliance to this guidance when submitting a Type II DMF for a drug product.	The commenters provided no rationale. Were the Agency to make the change suggested, the DMF format guidance should be changed by reference to require the same information to be included as in this guidance. This would be required to ensure a level playing field. However, this reviewer would recommend, if it has not already done so, that the Agency elect not to accept Type II DMFs in lieu of a drug product application as accepting DMFs is within the **FDA**'s discretionary authority..
II. A.	70-73	It would be useful if FDA could formally estimate when the updated drug substance Guidance would be published.	

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Section	Guidance Line	Comment / Observation	Rationale / Justification
II.	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. This reviewer would suggest that it would be simpler to change replace "active" with "contraceptive" and placebo" with "non-contraceptive."	None provided originally Though this reviewer has some concern with what the commenters have read into what is provided as an example, this reviewer would recommend changing that example from the draft's "**Similarly, separate P sections should be provided for an oral contraceptive with active and placebo tablets,**" to the equivalent, "**Similarly, separate P sections should be provided for an oral contraceptive with contraceptive and non-contraceptive tablets.**" In addition to removing the cause of the commenters' concern, the text reflects the reality that the "place holder" tablets in contraceptive systems often contain components that that are pharmacologically active but, in all cases, are non-contraceptive.
II.B.	161-162	Add clarification to confirm that the statement, and corresponding rationale, for not providing information for a P subsection should immediate follow the relevant section/subsection number	
II D.	216	PhRMA recommends that information contained in the DMFs be organized to follow the same format and content 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. If the commenters' prior text change were made to continue to allow the submission of Type II DMFs for drug products, the **FDA** should obviously make the changes suggested for DMF submissions.	For consistency. Clarification **See** reviewer's prior observation ands justification at **Row "68-70"** regarding Type II DMFs.
II.D.	236	A brief, one or two-sentence summary describing the dosage form and the container closure system is normally sufficient This reviewer mostly agrees with the comment made but, notes that the guidance requests a statement of the overfill under the "Container Closure System" heading. Based on the preceding, this reviewer would recommend retaining the outline structure in the draft.	The A and B sub headings are misleading in this case because they imply more detail than is actually required. Given the introductory comment (Lines 243-245) made, "**A brief description of the dosage form and container closure system and a statement of the composition of the drug product should be provided,**" this reviewer does <u>not</u> see how the "A" and "B" subheadings are misleading – all know that amount of detail needed often has little, or nothing, to do with the outline level of the request.

Section	Guidance Line	Comment / Observation	Rationale / Justification
II.D.	241	Reword Footnote 8 to more clearly state the level of granularity allowed vs. CTD format This reviewer understands the commenters' concern, but thinks that the concern expressed can be easily addressed by moving the italicized test to the end of the footnote and prefacing it with the modifier, "In addition:" "[8] Headings that are not followed by alphanumeric designations (i.e., non-CTD-Q headings) are included in this document for ease of providing recommendations on the information that should be included under a CTD-Q heading (in this instance *Description and Composition of the Drug Product (P.1)*. An application submitted in CTD-Q format neednot include these non-CTD-Q headings. However, once a particular approach is adopted, the same approach should be used throughout the life of the application. *In addition, an applicant can physically or electronically separate information under a CTD-Q heading as it chooses.*"	Clarification Reviewing the text cited, "[8] Headings that are not followed by alphanumeric designations (i.e., non-CTD-Q headings) are included in this document for ease of providing recommendations on the information that should be included under a CTD-Q heading (in this instance *Description and Composition of the Drug Product (P.1)*. An application submitted in CTD-Q format need not include these non-CTD-Q headings. *An applicant can physically or electronically separate information under a CTD-Q heading as it chooses.* However, once a particular approach is adopted, the same approach should be used throughout the life of the application," this reviewer finds the guidance is clear. **a)** The increased granularity in the guidance is provided to assist the applicant in structuring information under a CTD heading and, **b)** While <u>not</u> required to be included, can be if the applicant so chooses. Thus, the guidance permits but does not require increased granularity.
P.1	243-245	We suggest that unified terminology should be a potential topic for discussion at ICH level While this reviewer agrees in principle with this suggestion, in practice, this reviewer understands that, by proceeding, the **FDA** takes the lead in establishing a basis set upon which the ICH guidance can build. Thus, this reviewer suggests that the commenters' remark be ignored vis-à-vis expediting the issuance of this much needed guidance update.	We note that the requirement for CDER Data Standards Manual terminology contributes toward regional divergence. Factually, no **FDA** guidance can establish a requirement – that is why it is guidance; it simply proposes one suggested pathway to comply with the underlying regulatory requirements (in this case filing and **CGMP**). Second it is better to use a recognized standard terminology rather than to proceed without one. Since nothing prohibits other regions from using this reference, specifying its use does <u>not</u> *necessarily* contribute to regional divergence.
III.C. (P.1)	265 269	Change to: "In some instances, the composition of distinct subformulations (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." This reviewer <u>cannot</u> agree with the changes proposed because the guidance as written, does <u>not</u> specify separate tables (just list separately), and the examples do <u>not</u> show the information in separate tables.	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 substance is proportioned between the parts of the sub formulation. Since this guidance presents suggestions and <u>not</u> requirements, there is no need and the commenters present no "text supported" rationale to justify the change suggested. Moreover, the text proposed in the draft is rational, does <u>not</u> specify the separate listings must be in separate tables, and should, if followed, facilitate the reviewer's assessment of the applicants' submissions.

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Section	Guidance Line	Comment / Observation	Rationale / Justification
P.1	283-285	Concern has been expressed regarding the need to include tracer compounds 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 is not disclosed. This reviewer cannot agree with this proposal and would suggest that firms having such concerns generate and file proprietary mixtures thereof in a DMF submission. Done in this matter, those tracer mixtures become trade secret proprietary information and these can then be appropriately referenced by the sponsor in P.1 and P.3 to satisfy the applicable regulatory strictures and still provide increased assurance that that information will not be advertently or inadvertently disclosed.	The commenters provided no rationale. Because even the filing regulation requires the listing of the components as they do (**21 CFR 314.50(d)(1)(ii)(a)**) and makes no provision for the non-disclosure of such and, as the US Supreme Court has ruled on more than one occasion, no Agency administrator has the authority to recommend or to permit any divergence from any clear regulatory requirement, the Agency cannot legally comply with this proposal. Moreover, there already exists a mechanism in the Agency for dealing with "trade secret" information such as this. Based on the preceding, this reviewer would recommend that that alternative be explicitly "recommended" for such in this guidance. In this manner, both regulatory requirements and the commenters' concerns can be satisfied. Then, the sponsor will have the choice of how to proceed.
P.1	291-293	Separate tables of qualitative and quantitative compositions of mixtures should be optional. The applicant may choose to include the information in the standard composition tables. Since the text in the draft clearly indicates that said separation is optional, this reviewer does not understand why this comment was made.	The commenters provided no rationale. Factually, the text in question states (emphasis added), "**For ease of review, CDER and CBER prefer that the quantitative and qualitative composition of mixtures be included in the application in a separate table.**" Since the guidance clearly indicates that the text states a preference and not even a request, this is reviewer is at a loss to justify the commenters' remarks.
P.1	304 (Footnote 10)	Efforts to accept compendia in addition to USP/NF (for example, EP or JP) should be accelerated to provide global consistency This reviewer finds that this comment is, at best, a misguided and, as such, should be ignored.	Clarification Until the **FDC Act** is changed to recognize other official compendia, the footnote should be left as it is: "[10] **A compendial component is a component that has a monograph in an official compendium as defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j)).**" Reality should NOT be ignored. Moreover, the language proposed is particularly inappropriate because, as the commenters should know better than any other, the industry and not the **FDA** has more leverage with Congress – the only "agency" that can legally effect the change that this comment is espousing.

Section	Guidance Line	Comment / Observation	Rationale / Justification
P.1	302	Define more clearly what "official compendium" is, perhaps by example. Since the pertinent statutory reference is provided in the draft guidance, this reviewer is at a loss to see what more needs to be done, but, in the interests of serving this customer, suggests that the defining text be added to Footnote 10.	Clarification The statute (**FDC Act** at **21 U.S.C. 321(j)**) defines the term "official compendium" as follows: "The term 'official compendium' means the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them."
P.1	304-315	Reference to Quality Standard should be optional in P.1 since it is required in P.4. The reviewer is again at a loss here because all guidance sets forth optional requests and reference to the "Quality Standard" used in the testing is just as optional in P.1 as it is in P.4. The guidance text should therefore remain as it is	The commenters provided no rationale. Guidance requires nothing is only suggests. Moreover, it would have been helpful had the commenters proposed a solution that the commenters felt would address the concerns stated – perhaps a cross-referencing one. Lacking any proposed solution, the commenters' remark is <u>not</u> logically supportable on its face and, therefore, this comment should be discounted.
P.1	307-309	Generally, the applicant's code should not be listed Since the commenters' remark is a generalization supported by the guidance text in this instance, this reviewer cannot disagree with the statement. However, this reviewer is again at a loss to understand why the commenters felt compelled to make this comment to the guidance text proposed in the "References to Quality Standards" subsection of P.1.	The commenters provided no rationale. Based on the paragraph (**Lines 304-315**) containing the cited text, "For compendial components, the appropriate official compendium should be cited.[10] Compendial components should comply with the monograph standard included in the official compendium, and citation of the official compendium confirms compliance with this standard. The compendium should be cited even if an in-house specification that provides for more testing than that of the compendial monograph is used to evaluate the component. For noncompendial components, the type of standard used to evaluate the component should be listed (e.g., in-house standard, *Code of Federal Regulations* (CFR) citation, DMF holder's standard). The applicant specific numeric code (e.g., SPEC 311101.2b) of the specification used to evaluate the quality of the component should not be listed in the composition statement. The actual specification used for the drug substance should be provided in S.4.1. For the excipients, the actual specification should be provided in P.4.1 or P.4.6 and A.3 as appropriate," the commenters must be complimenting the guidance.

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Section	Guidance Line	Comment / Observation	Rationale / Justification
P.1	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. Though the confirmation you seek should come from the Agency and not this reviewer, the reviewer's short answer is that it depends on the what the "source" of that mixture – **a)** one that the applicant controls or **b)** one that is made by an independent manufacturer that holds the intellectual property rights for the "proprietary mixture: in question. The text in the adjacent column presents the supporting justification for this reviewer's answer. To treat "applicant-controlled proprietary mixtures" in a manner other than stated would subvert the regulatory process by permitting firm's to identify in-process materials, like premixes and mixes, as a proprietary mixture and, thereby, list the mixture's name and function without disclosing the components from which it was fabricated even though that information is in the control of the applicant. To the "we" who crafted this seemingly innocuous question, this reviewer doffs his hat.	The commenters provided no rationale. Given the text cited* in the subsection being commented on, it is clear to this reviewer that the applicant should state the function of each component that the applicant's firm adds to the formulation at any point in the manufacture thereof. The sticking point on "proprietary mixtures' is whether or not: **a)** they are purchased or **b)** manufactured by the applicant. In the first case, all that one need do is name the mixture and state its function (e.g., Kolarcan colorb lend N-1234, approved proprietary dye mixture for use in film coating. In the second case, the mixture, proprietary (or not) is not a component but an applicant-generated mixture of components. In this later case, each should be named and its function provided unless the firm treats such as "trade secret" items and generates and submits a suitable DMF for each one. Then, the applicant may simply name the mixture, provide a DMF-access authorization letter, and list its overall function without naming the components and/or providing their function in the application. Thus, when the applicant prepares (or contracts out the preparation) of a mixture of components that it represents are proprietary mixture, it is up to the applicant firms to choose which path they wish to pursue. * The function (i.e., role) of each component in the formulation should be stated. Components that are used in the manufacture of the drug product and do not appear in the finished drug product except at residual levels (e.g., some solvents) should be identified as processing agents.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.C. • Amount	332-335	Cross references are given either to the CTD section number, or the FDA guidance hierarchy. This makes it confusing and difficult to navigate the guidance. For clarity, we suggest that 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 Section V.B." This reviewer thinks that this is an excellent suggestion and, in the interest of "harmonization," suggests that the CTD style be used throughout with the referencing modification in the guidance that this reviewer has suggested or something like it.	The commenters provided no rationale. The use of a single self-consistent referencing system in a document is better than two quasi-independent referencing systems especially when one of them, the **FDA**'s outline structure is itself a combination of outline and bulleted referencing. To address the issue of guidance granularity below the level in the current CTD format, this reviewer would suggest simpling affixing the appropriate ".n" suffix to the next higher (least recognized level's) level's reference tag (e.g., if the lowest level CTD defined level's identifier is "P.2.1.1" then the appropriate guidance sub-level guidance sections, if any, could be identified as P.2.1.1.i (where i ranges from 1 to n). To indicate that they are a guidance addition, they could be set in a font whose height is not more than 90 % of that of the recognized identifier's font and a footnote with example added in the introductory text. (using the hypothetical P.2.1.1 example and presuming "n" is 3, the subsections added in the guidance would be identified as P.2.1.1.1, P.2.1.1.2, and P.2.1.1.3.
~~III.B.~~ III.C.	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..." In general, this reviewer concurs with the revision suggested but would, for completeness, suggest the following: **"For gaseous products (e.g, anesthetic gas mixtures), the amount ofe ach component should be expressed in volume per unit volume on a per liter basis.** For liquid products (e.g., injection products and oral liquids), the amount of each component should be expressed in weight per unit volume on a per milliliter basis. **For solid and semisolid products (e.g., tablets, ointments and suppositories) the amount of each component should be expressed in weight per unit mass on a per gram basis.**	The commenters provided no rationale. For completeness and to ensure that the basis requested for all types of drug products is explicitly stated, this reviewer suggests adding the additional text for gaseous, semisolid, and solid products.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.C.	334	Revise as follows: "... the target amount should be listed in the composition statement." This reviewer concurs.	The commenters provided no rationale. For grammatical correctness
III.C.	358	**Table 1 Example Target Composition Statement** We suggest that parenthetical text (such as % composition, which is a Canadian expectation) be added to the format. This reviewer disagrees, preferring instead to suggest that a table note "A" be added at the end of the title as shown: **Table I Example Target Composition Statement [A]** That note should be placed just after the end of the table and state: **"[A] To address requirements in other jurisdictions (e.g. Canada, EU, Japan and China), the applicant may add additional columns (e.g., one for the formulated percentage of each component in the drug-product unit). In addition, separate tables should be provided for each strength when it is appropriate to do so."**	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. This reviewer thinks that rather than introducing another column in this column that is not needed by the Agency for its reviews would be counterproductive and overly prescriptive. By placing the suggested changes in a table note placed as suggested, the commenters' concerns are addressed without adding significant additional complexity to the example that some might feel compelled to include though the Agency sees no need to request such. Because other jurisdictions do require such additional information, the table note provides the flexibility needed for "global consistency" without unduly burdening US applicants.
III.C. Example Table	358-359	Please clarify that, if an official compendium other than the USP or NF is also referenced in the NDA/ANDA, such as the 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 on other compendia can also be handled via an annual report. This reviewer cannot nor can the **FDA,** bound by US statute, accept the preceding request for clarification.	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. Given the reality that, by statute, the ONLY official compendia are the USP, NF and the Homeopathic Pharmacopeia of the United States, no other compendium can be recognized as official. Therefore, **a)** the Agency correctly requests such to be listed as "in-house" specifications and tests; and **b)** the commenters have correctly observed, *if such "in-house" specification or method is **tied** to the JP, JP-E, EP (PhEur), BP or any other FDA-recognized source,* a change in the referenced compendium would trigger the need of the NDA or ANDA holder to file a CBE or, in rare cases, could require a prior approval supplement. However, if the applicant's specification or method is developed from such a source, *but not tied thereto,* there would be no such need. The preceding is true of methods or specs from any other such FDA-recognized source.

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Section	Guidance Line	Comment / Observation	Rationale / Justification
III.C(P.1) V.B(P.3.2)	358 AND 769	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 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" This reviewer not only disagrees with adding the revision proposed but would also propose the text be revised to revised to read: "For example, **unless the applicant has established that particle size distribution has no effect on the** bioavailability, **drug-product uniformity and/or the stability of the active or actives,** drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution."	The commenters provided no rationale. This reviewer agrees that the effect on bioavailability needs to be considered, especially for actives that have very low solubility. However, in addition to dissolution rate, the effect of the particle size distribution on active uniformity and stability must also be considered. The commenters' revision does not do that. In addition, the note, while instructive, would make the guidance document less flexible than it should be – **a)** some may have other criteria and **b)** future developments may indicate that the criterion proposed is not valid. Based on the preceding, this reviewer proposes to revise the text as stated.
IV.A.2	437	We suggest that, for clarity, the term "functional excipient" should be defined in the Glossary. See glossary comments for proposed definitions. This reviewer disagrees.	Implicitly, "for clarity" is the commenters' rationale. Since all excipients in a formula serve some function, stating that the component is an excipient in the formula also defines it as a "functional excipient." Therefore, there is no need to define the term "functional excipient" because to do so in the context of this guidance would be equivalent to defining the term "excipient excipient."
IV.A.2	437-445	Eliminate reference to US- recognized ICH countries EU/JP This reviewer cannot agree because the **FDA** is charged with approving drug applications for the United States and has the duty to independently assess the safety of any drug (by law any component in a drug is a drug), including any excipient that it considers "novel."	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. First, the commenters' rationale contains nothing whatsoever that this reviewer can find that addresses their proposal. Second, as observed, given the **FDA**'s duty, the draft is properly stated.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.A.2 Excipients (P.2.1.2)	439-457	We assume that full CMC information is not necessary for flavors or food additives, which are not compendial. This reviewer disagrees; full excipient information should be provided for flavors and food additives used in drug products.	Clarification Because flavors and food additives may be harmful or adversely affect certain portions of the population, they should be handled as any other non-compendial excipient would be.
IV.A.2 (P.2.1.2)	447-457	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 pharmacopeia other than the U.S.P. as having adequate data packages to support reduced information in the filing. This reviewer disagrees.	Definition needed for clarity. This reviewer agrees and recommends that the term "novel excipient" be defined, as it is in the text with an additional statement that, "Any excipient that is not a 'novel excipient' is a 'non-novel excipient.'" --- The issue is not what should be the case but rather what is the case. Given the **FDC Act**'s definition of "official compendium" and the applicable **CGMP** regulations' clear language, the **FDA**, legally bound by both, cannot do as the commenters suggests. Moreover, that an item is listed in some pharmacopeia does not ensure that a given supplier of that item manufactured, processed, packed, held, tested and released it under a GMP that ensures its safety and fitness for use.
IV.A.2 (P.2.1.2)	468	Eliminate the word "any." This reviewer disagrees and, to ensure clarity of scope suggests that **Lines 470-472** be revised to read, "Information should be provided in this section of the application (P.2.1.2) when using any excipient (e.g., docusate sodium, caffeine, methionine), **regardless of whether it is novel or not, or compendial or not,** that has the potential to impart its own pharmacological effect.	It implies that non-novel excipients are also included in the scope, which may be an unnecessary burden for applicants [Text relocated to the "Rationale" column "where it should have been placed.] To eliminate any ambiguity and to ensure that all excipients that have the potential to impart their own pharmacological effect are uniformly addressed, this reviewer has proposed the revised text. Such information is important and should, if requested, be furnished.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.B. (P2.2.1)	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. This reviewer does not agree with either suggestion and recommends that, except as indicated in following reviewer recommendations, the text (**Lines 487 through 489**) should remain as it is.	The P.2.2 section is not intended to provide a comprehensive 'developmental history' of all work done during development, only the rationale for the development of the dosage products proposed in the application. Contrary to the commenters' assertions, the intent of section P.2 and hence that of section P.2.2 is as the FDA's draft "M 4" guidance outlines. Clearly more than a "rationale" is indicated; equally clearly, based on the commenters' remarks alone, more than a "rationale" is needed.
IV.B. (P2.2.1)	490-493	Revise as follows: "For modified … ad ~~-etailed~~ description of the release mechanism. For novel delivery systems a development summary of the new mechanism should be included." For the reasons presented in the justification, this reviewer opposes this revision. This reviewer suggests the following change be considered: "For modified … a detailed description of the release mechanism. For ~~novel~~ **the proposed** delivery ~~systems~~ **system,** a development summary of the ~~new~~ mechanism should be included.	The commenters provided no rationale. First of all, the text that the reviewer proposes to revise, **"For modified release drug products, a detailed description of the release mechanism (e.g., erodible matrix system, barrier erosion, diffusion) and a summary of the development of the release mechanism should be included,** should address both non-novel and novel mechanisms. Second, to ensure that the applicant truly understands the mechanism it states is "properly understood," the description of said release mechanism should be spelled out in detail. Third, the Agency should consider changing the request to request a summary of the development of all release mechanisms proposed by applicants, not just the novel ones, should be provided again to ensure that the Agency understands the approach to its development that the applicant actually used.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.B.1	495-499	Revise as follows: "The differences between clinical formulations **used_in pivotal studies** and the proposed formulation described in P.1 (i.e., composition statement) should be discussed. This reviewer agrees that the wording needs revision but would recommend that the sentence in question be revised to read: "The differences between ~~clinical~~ the formulations used in pivotal studies **(clinical, bioequivalence, and primary stability)** and the proposed formulation described in P.1 (i.e., composition statement) should be discussed."	We recommend adding "used in pivotal studies" after clinical formulations and clinical batches since data from early clinical studies may not be appropriate. First, this reviewer agrees that the formulations used in all pivotal studies should be included and that bioequivalence studies should be included because they are the pivotal studies in most ANDA applications. However, this reviewer thinks it should be left up to the assigned FDA review team to determinewh ich clinical batches it needs to include here.
		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. This reviewer objects to the inclusion of the word "significant" here because this injects an unneeded subjective element into an otherwise objective request. Moreover, provided the preceding sentence is revised as this reviewer proposes, this would propose changing this following sentence to read, "Any changes between the proposed commercial formulation and those formulations used in **the aforementioned pivotal** bathes should be clearly described and a rationale provided for the changes."	What is "significant" depends on the subjective viewpoint of the person and, *a priori*, the viewpoint of the applicant and that of the Agency application reviewers is different. Moreover, the differences concerning "significance" can and do slow down the review process For that reason, this reviewer knows it would be better not to insert "significant" into the text at this point. Moreover, since it would be better to introduce the terminology in the first sentence, as the reviewer proposes to do, and then change the second sentence in the manner shown.
IV.B.1 (P.2.2.1)	503-505	Modify sentence two as follows: "**Where appropriate**, a summary of the development of an in vitro/in vivo correlation ..." While this reviewer thinks that a modifying clause is needed here, this reviewer proposes the following alternative, "**Unless no such studies are conducted**, a summary of the development of an in vitro/in vivo correlation ..."	No rationale was provided by the commenters. The inclusion of a modifying clause is only needed when no such studies were conducted. Since there is no need in such cases for the non-specific, "where appropriate," the prefacing phrase, "Unless no ...," is more appropriate and should be used.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.B.1 (P.2.2.1)	511-512	Appropriate data to support scoring should be included in the submission. This reviewer disagrees and finds that the text here should remain, "Data to support scoring should include content uniformity and dissolution studies comparing split versus whole tablet.[12]"	The commenters provided no rationale. The commenters' alternative, by failing to specify what data are appropriate, is at odds with the **FDA**'s clear guidance on this issue. In addition, since the commenters provided no rationale for the change, and it is less clear and not aligned with the **FDA**'s specific guidance, this unidentified change should be rejected.
IV.B.2 (P.2.2.2) -and- III.C.	529-539 341-343	Overages should only be listed in the batch formula and not in the composition statement. This reviewer does not agree with the commenters' statement. The draft text should be retained with appropriate modification to read (Lines 531-539), "An overage is a fixed amount of the drug substance in the dosage form that is added in excess of the label claim. Any overages included in the formulations described in P.1 should be justified. Information should be provided on the: **(1)** Amount of overage, **(2)** Reason for overage (e.g., **a) comply with 21 CFR 211.101(a)**, **b)** compensate for expected and documented manufacturing losses, **and c)** ensure proper dose delivery **[an amalgam of post-release issues associated with reconstitution; deliverable "doses" for non-solids and gaseous or powder dispersions; and stability], and/or reduce the number of drug-product assay determinations for each batch needed to ensure that the requirement set forth 21 CFR 211.101(a) was met**), and **(3)** **A *scientifically sound*** justification for the amount of the overage. The overage should be included in the amount of drug substance listed in the composition statement (P.1) and the representative batch formula (P.3.2). In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend the expiration dating period, is not appropriate."	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 the associated definitions in the glossary would be useful. Manufacturing overages are utilized to achieve the target amount reflected in the composition statement and the 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 a composition statement. We suggest removing the example of "ensure proper dose delivery" from this section. First, the commenters' first two remarks, while laudable, do not address the issue raised. The commenters' third remark does bears on the issue of reflecting overages in the composition statement (Lines 341-343). However, the fact is that the overages listed are the theoretical targets and, when the active is not 100 % pure or a salt of solvate, must be reflected in the amount of substance to add over and above the theoretical amount. The commenters' last two remarks are again off the mark. Based on the factual realities of the nature of the drug substance vis-à-vis the active, the overages appertaining thereto should be appropriately addressed in both places. [**Note:** Though not relevant to the issue at hand, the obvious answer to the "how" portion of the commenters' "It is unclear how, and for what reason, an overfill would be reflected in a composition statement" is in a footnote. Moreover, this reviewer knows that the example of "ensure proper dose delivery" should also be retained as this reviewer's proposed text clearly explains.]

Section	Guidance Line	Comment / Observation	Rationale / Justification
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 provide information concerning equipment used to produce "clinical" batches of drug product. This reviewer disagrees, does not understand why the commenters' remarks focused on only one-forth of the items requested in the table, and, with the modifications suggested, thinks that the text should simply be revised to read, "A table should be provided that compares: **a)** the equipment used to produce clinical batches that support efficacy **in an NDA application and/or batches that support** bioequivalence in an ANDA and the primary stability batches **to:** **b)** the equipment proposed for production batches. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (P.5.4). The table should identify (1) the identity (e.g., batch ~~number~~ **code**) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch # 5851234), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).	This section is an example of information considered excessive for conventional dosage forms. Factually, tabular data is easier to review than uncollated text passages. Where the applicants places the focus (by the way they structure the tables is up to them – they can place the differences they think are critical at the front of the tablular data requested. With respect to the commenters' last comment: Since few submit testing on a sufficient number of batch representative units from any batch much less from a commercial one where the results from upwards of 300 representative units are needed to characterize the **batch** in most cases, the commenters' assertions about batch equivalence are, at best, wishful thinking. The commenters' rationale, "This section is an example of information considered excessive for conventional dosage forms," is an unsubstantiated statement that does not address which information is excessive, why it is it excessive, or even what are the commenters' "conventional dosage forms." Thus, *regardless of the apparent differences or lack thereof*, the applicant should submit a table that compares the equipment used in the key submission batches specified to the equipment proposed for the production batches. Notwithstanding the permissions conveyed by SUPAC, the applicant bears the burden of proving what they are proposing to do is similar enough to what has been done to ensure that there is little or no risk of significant drug-product uniformity changes between the equipment and scale that has been used and the equipment and scale that the applicant proposes to use for full-scale production. [**Note:** This reviewer (having some experience with formulations ranging in scale from 0.75 cu. ft.[0. 02 cu. m] to 175 cu. ft. [5 cu. m])h as been in several situations where a firm **a)** failed to recognize the negative impacts of scale on materials and **b)** found that simply scaling up the production process, while "permitted by SUPAC," produced drug-product batches that failed to meet the drug product's in-process and/or release specification even when the testing of a few samples indicated that they did.]

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Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.D. (P.2.4)	589 (entire section)	D. Container Closure System (P.2.4) This section could be written more clearly. Perhaps simply reference applicable guidance already in existence. This reviewer agrees with the commenters' first remark, but is at a loss when it comes to the second since a boxed reference to current FDA guidance is contained at the end of the section (Line 619).	Clarity The section in question does provide a reference to the "applicable reference guidance already in existence." The guidance provides that reference in a text box as it consistently does throughout the document – perhaps this was overlooked..
	596	A brief description of the container closure system 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 If the suggested text is solely to replace the text in Lines 596 and 597, "**A brief description of the container closure systems listed in P.7 and the container closure system used for storage and transportation of protein drug products should be provided,**" this reviewer supports it. However, if it is intended to replace more than that one sentence, the reviewer does not agree.	Since no separate "rationale" is provided, this reviewer will presume that it is "clarity. However, by only referencing the beginning line number ("596") it is unclear what the scope of the proposed change truly is. This reviewer would suggest that, in the future, the commenters should include the line range whenever the proposal to change text addresses text that extends beyond one line.
~~VI.F.~~ IV.D.	598	This guidance 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. Lacking any specifics as to what specific topics the commenters meant, this reviewer cannot evaluate the value, if any, of what the commenters have said.	Specifics including DEHP labeling requirements are better placed in the guidance Container Closure Systems for Packaging Human Drugs and Biologics (May 1999) Given the non-specificity of the comment and the obtuseness of the rationale, this reviewer cannot evaluate the value of the statements made and must therefore discount them.
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, email etc) of a contact person for PAI are administrative information already provided on the Form 356h. They do not need to be included in the CTD section P.3.1 Manufacturer(s). This is not consistent with the spirit of global harmonization. This reviewer disagrees.	No supporting rationale provided other than the "already elsewhere" and the "ad miseri cardium refrain, "not consistent with the spirit of global harmonization" in the comment. For obvious reasons (of which this reviewer is certain the commenters are well aware) this request is appropriate for the purposes intended – to speed PAI inspection prep, scheduling and execution – a goal the commenters claims to support.

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Section	Guidance Line	Comment / Observation	Rationale / Justification
V.A. (P.3.1)	692	It is not clear why building numbers are being requested. This reviewer disagrees	No supporting rationale was provided. As a some times auditor of multi-facility foreign campuses, knowing the layout of such multi-facility campuses is invaluable in scheduling a time-efficient audit that minimizes inter-building time losses. Perhaps knowing this, the commenters will no longer question the inclusion of this text, but instead support it.
V.A. **Mfg.** (P.3.1)	710-713	We strongly suggest that these lines be removed: ~~"do not agree with the statement, "Facilities should be ready for inspection when the application is submitted to the FDA". For all NDA's and BLA's the applicant indicates when the facilities will be ready on the 356h. It is our understanding that the readiness at the 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 the 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 supplement and priority applications."~~ This reviewer rejects the commenters' remarks because they are at odds with one simple reality – **UNTIL a sponsor KNOWS (<u>not</u> thinks or believes but, *by on-site, second-party or third-party audit using competent CGMP-knowledgeable auditors*, knows) that all referenced suites are <u>truly</u> ready for inspection, the sponsor should NOT file that application.**	This is not relevant to the scientific content of the application. May need to be reconsidered with the FDA quality initiative. The commenters' comment and rationale ignore several realities. The date of filing of an application is completely and totally within the applicants' control – if <u>not</u> ready for any facet of the review of their application, they should <u>not</u> file it. Second, if an sponsor commits to a date on a 356h, then given the FDA's policies, it is illegal for a firm to submit the CMC section of an NDA or ANDA filing before that date unless that facility is truly ready for inspection (to do so would be to make a false statement to an FDA official acting on behalf of the United States). Third, the commenters' remarks concerning their "understanding ..." and "willingness to discuss ..." do <u>not</u> bear on the issue of readiness at filing. Moreover, the commenters' next remark overlooks the reality that an applicant is permitted to file the CMC section of an application 90 to 120 days before the filing date for the rest of the application (**21 CFR 314.50(d)(1)(ii)(*b*)(IV)**) so if the CMC section were so filed, today's science- and systems-based ISO-guided FDA inspectorate (committed to scheduling inspections based on the date that the CMC section is filed) could well be requesting PAI inspections prior to the applicant's decision to file the rest of the application (the application's official filing date). Next, since the commenters agree to be **ready for inspection** for manufacturing supplements and priority applications, they should get with the program and be ready when they file. If all were ready at filing, then the countless FTEs the Agency wastes every year contacting unready sites would be available for constructive use.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.A. (P.3.2)	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. This reviewer disagrees and notes, *as in the example*, additional standards may need to be referenced in the batch formula. In addition, the commenters' comment is again at odds with the industry's stated goal of expediting the review process.	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. Because different reviewers may be assigned to review different parts of the CMC to speed the process, it makes sense to again provide the "reference standards" information. – if the industry truly wants an expedited review process any valid "PERT" review of the application review process will clearly find that reviewing certain sections of the CMC section in parallel is: **a)** much more elapsed-time efficient, **b)** a better utilization of resources and **c)**, if properly done, can improve review morale by better aligning the talents and special interests of the review staff with the tasks assigned (for example, the clerical staff can be assigned to check for the presence of every section and flag every apparent discrepancy without having to understand what they are checking and, thus, reduce the boredom factor for those whose principal job is to evaluate the correctness and import of the content). [**Note:** When this reviewer directed laboratory operations, he found that giving the staff what they requested to help them do their job improved productivity – he finds it odd indeed that the industry would resist giving the Agency what little this guidance asks for from the sea of information generated in support of an application. This productivity improvement was the case because the staff knew exactly what they needed much better than this reviewer did or could because they did the job every day.]
V.A. (P.3.2)	720	Replace "intended validation batch sizes" with "intended commercial batch sizes" This reviewer agrees.	For processes with multiple unit operations that are subsequently combined, i.e., combination of multiple granulations by subsequent blending or combination of coating pan operations, the validation scale may not necessarily be the same as the intended commercial scale. The commenters' detailed, clear rationale seems valid. However, this reviewer *would recommend adding a footnote that clearly states the size and number of validation batches* [**subject to the constraint: *the number of validation batches must collectively be sufficient to produce NOT LESS THAN three (3) intended commercial-scale batches unless a written waiver is obtained to the FDA's "NLT 3 validation batches" policy***].

Section	Guidance Line	Comment / Observation	Rationale / Justification
V. Mfg. (P.3) **A. (P3.1)** **B. (P.3.2)** **References to Quality Stds.**	759-761	Replace the word "actual". We suggest that reference to quality standards 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. This reviewer disagrees, given the reality that the rest of the comment does not apply to the "actual specification" issue, now understands the importance of this request, and recommends that the test be placed in a separate bullet as follows: " • **Specifications** The applicant specific numeric code (e.g., SPEC 101.2b) of the specification used to evaluate the quality of the component should not be listed in the composition statement. The actual specification used for the drug substance should be provided in S.4.1. For the excipients, the actual specification should be provided in P.4.1 or P.4.6 and A.3 as appropriate."	"Actual specification" is open to interpretation. While, the definition of "actual specification " may be unclear to the commenter, it is crystal clear to this reviewer. If the objection is based on "interpretation," then this reviewer would recommend that the term be added to the Glossary and defined as follows: "**Actual specification**: The specification that the applicant actually uses for the drug substanceo r component for a given analytical test or examination. For example, the compendial specification for the pH of an ingredient might be '4.0 to 7.2,' but the applicant's actual pH specification for that ingredient is '4.3 to 6.9.'" The commenters' second comment has little to nothing to do with the issue of specifications. The commenters' third comment addresses the sentence before the test in question. The commenters' final comment is again wide of the mark. Based on the preceding, modified as proposed, the current text should be incorporated into the final CMC guidance.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.1 (P.3.3)	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. This reviewer disagrees and notes that *if the comment were taken literally,* **the flow diagram and description of the process would contain no information.** Based on the reality of the need to cover all **CGMP**-regulated areas, the routine manufacturing unit operations addressed by **CGMP** start with: **a)** receipt of components; **b)** sampling of components; **c)** testing of components, **d)** results evaluation and release of the passing components **e)** controlled issuance of a batch for manufacture (batch scheduling) **f)** allocation of the released components assigned to the scheduled batch; **g)** start of production of a batch; **h)** in-process control of the first phase of manufacture by **1)** charging the assigned components into the assigned vessel; **2)** performing the processing required **3)** as the processing step is being conducted (or at the end) taking batch representative samples **i) – k)** testing and/or examination, and release of the output of first phase in the manufacture of a batch to the next phase; and end with unit operations: **ia) – ic)** examination or testing of the drug product samples, results generation and review and release of the batch; and **id)** transfer of the released drug-product batch from manufacturing to warehousing and/or distribution.	No rationale was provided. Since **CGMP** covers all aspects of manufacturing from incoming, through in-process, to release and distribution, the flow diagram needs to be expanded and, not as the comment indicates, contracted. Whereas **a)** the CMC section of an application must be CGMP compliant or the application should not be approved by the Agency as the Agency would be approving the manufacture of adulterated drugs (**21 U.S.C. 351(a)(2)(B)** and **21 CFR 210.1**) and **b)** the general areas to be covered are addressed both in **21 CFR 210.3(b)(12)** and in the headings in **21 CFR 211**, any CGMP compliant flow diagram must address all CGMP-controlled areas *including weighing* (e.g., 21 CFR 211.101 Charge-in of components) as a controlled unit-operation (e.g., **21 CFR 211.101(b)**) within the whole of **CGMP**-compliant generation and release of a **CGMP**-compliant drug product. Moreover, the requested diagram (which may be composed of a series of "sub" diagrams) and description of the manufacturing process should address all regulated manufacturing unit operations. Since that is the case, all CGMP-regulated unit operations should be appropriately included in said diagram or set of "sub" diagrams.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.	784	Revise as follows: "A flow diagram should be provided giving the steps of the process and illustrating the movement of the components into and the movement of product out of the manufacturing process ~~and showing where materials enter the process. The entire manufacturing process should be depicted (e.g., weighing …)~~" This reviewer disagrees with the revisions proposed and suggests the following (**Lines 784 – 797**), "A flow diagram should be provided giving the steps of the process and showing where materials enter **and exit** the process. The entire manufacturing process should be depicted (e.g., ~~weighing~~ **receiving** of **incoming** components through finished product release **to released drug product holding and distribution**). The flow diagram can be supplemented with information presented in tabular form, if appropriate. The flow diagram should include: • each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e., ~~noncontinuous~~ **discontinuous** process) before the next processing step is performed • the material **or materials** being processed • **the point in the step where the material enters the step and, if it exits the step, the point where the material exits the step** • critical process controls and the points at which they are conducted • the type of equipment used (equipment model number is not needed)"	Clarifies what should be included in the flow diagram. Factually, the changes proposed CHANGE what the commenter(s) think should be included in the flow diagram just as the last comment attempted to do. In addition, the text paragraph beginning at **Line 784** and continuing to **Line 797** actually states, "A flow diagram should be provided giving the steps of the process and showing where materials enter the process. The entire manufacturing process should be depicted (e.g., weighing of components through finished product release). The flow diagram can be supplemented with information presented in tabular form, if appropriate. The flow diagram should include: • each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e., noncontinuous process) before the next processing step is performed • the material being processed • critical process controls and the points at which they are conducted • the type of equipment used (equipment model number is not needed)" The modifications proposed limit the scope of the manufacturing process to only those steps that the commenter(s) deem to be appropriate to include even though **CGMP requires** complete coverage of every regulated step. **The process diagram should cover the process as CGMP defines it** and neither as the FDA nor the commenters commenting here. **(See Row "782-797.")** For all of the preceding reasons, the revisions proposed by the commenter(s) should be rejected and those proposed by this reviewer implemented to align the scope of the guidance language with the scope required by **CGMP.**
V.C.	787	Revise as follows: "The section of the flow diagram which details the actual manufacturing or compounding should …" This reviewer disagrees and proposes (**see Row 784**) to leave that sentence unchanged.	Clarifies in what section of the diagram this information should be included. Under the guise of "clarification,' the commenter(s) remarks again attempt to change and limit the text in a manner that reduces its scope to exclude much of what **CGMP** requires to be covered.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.	790	We propose that FDA consider the following concerning critical *steps*. *Critical steps* (an ICH term) are defined by the development activities. For critical steps an operating range and an outcome has been demonstrated outside which a batch cannot continue. For the reasons stated, this reviewer disagrees with both of the preceding "concerning critical *steps*" statements in the commentary.	No rationale was provided. Factually, the commenters' first statement is not correct. Developmental activities do not define a step nor do they define a critical step. Technically, the developmental activities establish the steps and identify which are critical. The data from each step is then used to define the appropriate controls (active and passive) and the specifications for the control tolerances allowed on the step as well as the specifications for what constitutes an acceptable outcome from the execution of a given step (usually expressed in drug product manufacturing in terms of a material specification). Properly, CGMP defines what is critical and not the ICH, the industry, the FDA or this reviewer. As stated in this reviewers response to the **General Observation 1**: This reviewer can easily define the adjective "critical" in a manner that precludes the need to define the specific phrase "critical step." By statute (Federal Food, Drug, and Cosmetic Act as amended [**21 U.S.C. Title 9**]) and by legally binding regulation (**21 CFR 210.1**), ***critical*** means *"required to be controlled in a manner that complies with, or pertaining to any requirement specified in, the drug CGMP as set forth in **21 CFR Parts 210** through **226**."* This is the case, because, as **21 CFR 210.1** states (emphasis added): "(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. (b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply,s hall be subject to regulatory action" **failure to meet any of the minimums established adulterates** the **drug** and **subjects** the **person responsible to criminal** regulatory **action.**

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C. (Cont.)	790 (Continued from previous page)	**(Comment/Observation, Continued)** A step is NOT critical if it can be adjusted, and/or stopped for adjustment, based on results of in-process testing without any implication on the quality of the part processed material or finished product. *By definition*, the commenters' third "concerning critical *steps*" statement is not valid. A critical step is not associated with a business/producer risk; ~~Critical steps in manufacturing processes are typically rare~~; This reviewer disagrees with the preceding because it is patently false. they are company defined. This reviewer disagrees Based on the justifications provided, the preceding commentary should be discounted.	**(Reviewer's justification, Continued)** Therefore, anything required by **21 CFR Parts 210** through **226** is obviously "critical" to those that manufacture drugs. Any entity that falls outside of the clear requirements set forth in **21 CFR 210** through **21 CFR 226** or any thing that is above the minimums established therein is, therefore, a "**non-critical** entity (e.g., test, step, phase, control)." Contrary to the commentary provided, almost all critical steps have a clear business/producer risk associated with them. This is the case because **1.** The scientifically sound and appropriate setting of the limits on all specifications requires the use of statistics. **2.** The statistics used are based on the those that have variable risk and confidence levels that, in today's world, the applicant is allowed, within limits, to arbitrarily set (typically, for variable tests, if sufficient batch-representative samples are tested, the risk levels are set somewhere in the range from 1 % to >10 % and the confidence levels chosen are "90 %" or "95 %" the risk and confidence levels. [**Note:** When non-batch-representative samples are tested or too few batch-representative samples are tested *as some seem to do* without establishing the scientific soundness of the choices they make (for: a) representativeness for the distribution of the samples sampled; b) the number of samples tested, and/or c) the validity of the specifications established for testing a few units vis-à-vis the post-release lifetime expectations imposed on all in-commerce articles by the **FDA** (for NDAs) and/or the **USP** (for ANDAs) the real risk levels are generally difficult to estimate but, based on distribution-free statistics and the small number of discrete samples tested in-process and at release, the confidence levels are less than 25 %.] **3.** Moreover, the **decision model** typically **used is based on an estimate of the producer's risk** (that an accepted batch will subsequently be found to fail). The critical entities are defined by **CGMP**; the company only defines the nature of the steps and establishes controls and specifications it proposes to use as required by **CGMP**.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.1	790-796	A more precise definition of a noncontinuous process is needed. This reviewer does not agree with the preceding remark and recommends that the "noncontinuous" be replaced with the "discontinuous," which, unlike noncontinuous appears in the dictionary and its definition fits the type of process being addressed. 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. This reviewer can agrees with this comment if, by "appropriate," the commenters mean "predefined." With all of the preceding in mind, this reviewer suggests that **Lines 790 – 793** be revised to: • each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for an **extended** period of time (i.e., a **discontinuous** process) before the next processing step is performed	No rationale was provided. Given that CGMP requires the holding of in-process batches (**21 CFR 211.110(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or *after storage for long periods.*** [emphasis added) until approved for further processing by the quality control unit (QCU), most processes are non-continuous. What seems to be meant is, therefore, "might be held an extended period of time prior to the next step." Thus, the word "noncontinuous" should be replaced with the word "discontinuous."
V.C.1	796	Type of equipment used should be replaced with operating principles and design as defined in SUPAC Equipment. This reviewer thinks that the commenters have the beginnings of an excellent suggestion. Instead of replacing the text, the text should be revised as follows: • **the type of equipment used (equipment model number is not needed)** and its operating principles and design (as per the current official SUPAC Equipment section)"	No rationale was provided

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.2	809	Eliminate the need to provide working capacity of the equipment. This reviewer disagrees and would suggest augmenting the text to provide all of the information needed to judge the importance of material scale factors as follows: "**Equipment should, at least, be identified by type (e.g., tumble blender, in line homogenizer) and**, where relevant, **working capacity** (volumetric and mass). For tumble blenders and other equipment where working volume is relevant, the percentage of the working volume and that of the weight at the start of each step as well as at the end of each step using that equipment."	We do not believe there are situations when working capacity would be relevant. Having worked with blenders with volumetric working capacities of from 0.02 to 5 m^3, this reviewer knows that working capacity is relevant and that, in addition, the percentage of the working volume used at the start of any operation and that found at the end as well as the starting mass (weight) and the weight at the end of the step are all relevant factors. Moreover, contrary to the flexibility permitted by SUPAC in setting batch size, the practical reality for blenders is that they have fairly narrow effective working ranges. For example, the *effective* working ranges for tumble blenders are, in almost all cases, close to the 50 % of the blender's nameplate working capacity.
V.C.2	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 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. This reviewer thinks the commenters' suggestion is a good one but would suggest revising the wording slightly as follows, "...should be provided regarding **the** control measures (such as sourcing, manufacturing processing conditions, and the nature of the tissues) used to minimize the risk of TSE **contamination**.	Provides for explanation of exception. The modifications suggested: **a)** improve the grammatical correctness and **b)** correct the "risk of" statement to reflect the risk being controlled, "TSE **contamination.**"

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.2	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. This reviewer disagrees (**see** reviewer's response to commenters' **General Observation 1**) and the justification provided here.	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 tests (line 850, 867) is excessive and unnecessary. The comment section objects to the reality that, under **CGMP**, if a test or examination is "non-critical," then that test is a test that is not conducted routinely. The commenters' rationale is illogical and the examples support the criticality of the test under **CGMP** – for example, at some point the LOD meets the criteria established for the drug substance and the material is accepted; until the LOD is acceptable, the material is "rejected" and drying continued The preceding is the case because it is process critical that the drug substance be dried until it is within the specification established or the drug substance must be kept (rejected) from being transferred from the current step into the next. A comparable drug product example would be the adjustment of the pH of a solution. It too is critical because a) it must be adjusted and b) the adjustment must be to within some predetermined range before processing can continue. In the solution example, if the pH is not critical,t he process will not have an in-process control (pH adjustment) and a check of the pH for informational and trending purposes would be an example of a non-critical test, unless it is a control required to be done on every batch for some other purpose (or it is a PQIT, if only done periodically). Therefore, *contrary to the commenters' argument*, all in-process controls *and examinations* for which there are established criteria for acceptance that the material or drug product must meet before it can proceed to the next phase are critical (**CGMP**-compliance mandated) process controls and these should be treated as such.

Section	Line #	Comment / Observation	Rationale / Justification
V.C.2	843	We recommend including examples of process tests This reviewer does not object to this and would suggest that clear examples are needed that cannot also be confused with or, in some circumstances also be an in-process test. The following three clear examples come to mind: 1. Monitoring of the cleanliness of a vessel after cleaning has been completed to insure that it is clean enough for use in the production of another batch of material. 2. The clearance test for a packaging line to insure that all items from the previous packaging operation before allowing the next batch to be packaged to be brought from its staging area onto the line for the start of packaging. 3. The acceptance testing for an incoming component.	To help distinguish process tests from in-process tests. The fundamental difference between in-process and process tests are that the former are conducted during the processing step and the later are conducted before or after a process step (phase) has been completed. Both are covered by CGMP whenever they: a) must be done on every batch and b) must meet a specification or limit (quantitative or qualitative) before the operation in question can be started or, if started, considered to have been completed for each batch. To aid in understanding what is critical with respect to in-process (and process) testing (and examination), this reviewer suggests that the commenters carefully read all of **21 CFR 211.110** starting with the title "**Sampling and testing of in-process materials and drug products**" until they truly understand this section Then, they should carefully read **21 CFR 210.1** in a similar fashion. Finally, they should carefully read **21 CFR 211 Subpart I** as if its title, **Laboratory Controls**, were simply, "**Controls.**"
V.C.2	849-852	Revise to read as follows: "Steps in the process should have the appropriate 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). This reviewer disagrees; the text should not be changed to omit ", or otherwise," (non-critical and PQIT process controls). The text should remain: "**Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All process controls, critical or otherwise, 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 may be in place to monitor process yields or efficiencies. They may be added or deleted during routine production and should not require regulatory action to change. If a test or examination control, in-process or otherwise or manual, semi-automated, or fully automated, is required to be conducted during the production of each batch and it is required to meet some quantitative range or limit or some qualitative state, then that control falls under CGMP and it should be included in the description of the process. These include yield and yield % (**21 CFR 211.103**). [Collectively, the critical in-process and process "each batch" controls for the process.] [**Note:** Provided they are based on *sound statistical science*, a firm may establish and submit a *hierarchical control plan* (that spells out the conditions and controls for the switching among contingent levels of inspection (sampling and testing) to minimize the need for regulatory action.] In addition, to ensure that the manufacturing process is fully and properly described, all other controls need to reported.

Section	Line	Comment / Observation	Rationale / Justification
V.C.2	852	Add the following after the period: "Process steps and associated controls specified in the narrative that may have a major or moderate on the quality of the drug product are classified as critical. Other process steps and controls specified in the narrative are deemed to have minor or no impact to product quality. This reviewer cannot agree with the addition proposed because it violates several **CGMP** requirements. --- 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." This reviewer does not think that this addition should be included for the reasons stated.	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. The **CGMP** requirements define what is critical and the Agency should refrain from proposing guidance that is at odds with **CGMP** because **a)** they have no legal authority to do so and **b)** proposing guidance that is at odds with the clear requirements of any **CGMP** regulation is a subversion of the regulatory process. --- The guidance is supposed to address all of the issues associated with preparing and filing the CMC section of an application. The text addition proposed by the commenters has no bearing on the topic of the guidance. Moreover, the second guidance cited (Comparability Protocols [February 2003]) exists only in draft and, as such, should not be cited in any other guidance because it may never become final.
V.C.2	867-875	Revise to read as follows: "All critical process control 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 control should be located in applications submitted in CTD-Q format is provided in Figure 1." This reviewer disagrees; the draft text should be slightly modified (highlighting the changes): "All in-process material tests and any of the operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified as critical 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. All in-process material tests are considered critical process controls by definition because they directly assess the quality attributes of an in-process material and ultimately lead to a decision to accept or reject the in-process material or drug product. A summary (of where the information on drug product quality controls should be located in applications submitted in CTD-Q format) is provided in Figure 1."	No rationale was provided. First, the changes are at odds with CGMP. Second, the changes omit non-critical in-process controls, operating parameters, environmental conditions, process tests and the key phrase "that ensure each critical manufacturing step is properly controlled." Omits the working consideration of all in-process material tests as critical process controls by definition. On the positive side, the change from "... in the flow diagram and description ..." to "... in the flow diagram and in the description ..." improves the readability and the grammatical correctness of the text. The reviewer's proposed change to place the text, "of where information on drug product quality controls should be located in applications submitted in CTD-Q format," in parenthesis, "()" and insert "the" before "information" are proposed to increase text readability.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.C.3	887-912	Although narrative definitions are given for reprocessing and reworking, the glossary should contain definitions of these terms This reviewer agrees that these terms should be included in the Glossary.	Clarity Properly, the justification should be "for consistency."
V.D (P.3.4)	920-930	We suggest adding a provision here for applicants to include a justification for providing interim acceptance criteria for in-process controls. Whileth is reviewer knows that the current language, effectively "all ... acceptance criteria," encompasses all subcategories, this reviewer would propose the following additions if and only if the Agency thinks that the commenters' concerns should be addressed In this section of the application, all critical process controls (see section V.C.2) and their associated numeric ranges, limits, or acceptance criteria, **including interim acceptance criteria and hierarchical inspection and acceptance criteria schemes,** should be identified and justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section (P.3.4) as well. For critical operating parameters and environmental controls, numeric ranges, limits, or acceptance criteria typically can be based on the experience gained during the development of the manufacturing process. (See section V.E for possible exceptions when process validation information is warranted.) Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in P.5.4) should be provided as part of the justification. Additional information should be provided in this section (P.3.4) under the following circumstances."	No rationale was provided. Since text covers all acceptance criteria, there is no need to include any subclass thereof. However, to address the commenters' concerns, the text could be modified to address the less than common subclass "interim acceptance criteria" could be addressed by adding a modifying phrase, "including interim acceptance criteria." For completeness, the other less than common subclass "hierarchical inspection and acceptance criteria" should also be included.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.D (P.3.4)	927	Remove the parenthetical material beginning at the end of this line. This reviewer disagrees for the reasons stated.	Relevant batches to establish critical process controls do not ordinary equate to all batches listed in 5.4, only a limited pool from P.5.4 would be used to establish critical process control values. What is being requested is for the applicant to share the critical process control values found from the batches cited as a justification for those control criteria chosen. This is being requested to facilitate the application reviewers' ascertaining the degree that the criteria established are *scientifically sound* and *appropriate*. The commenters' rationale confuses "using relevant batches to establish acceptance criteria" with, *what is requested here*, "providing historical acceptance-related data to support the application's justification of the acceptance criteria proposed by the applicant.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.D (P.3.4)	947-950	The new guidance states: 'when the same analytical procedure is used for both the in-process and the finished product test, the acceptance criterion for the in-process test should be identical or tighter than the acceptance criterion in the finished product specification." We recommend that this section be reworded as follows; "when the same analytical procedure is used for both the in-process sand 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 drug product." This reviewer disagrees with the commenters' proposed changers as they effectively say nothing, but does agree that the text should be modified to make it agree with reality, as follows: "When the same analytical procedure is used for both the in-process test and the finished product test, **the acceptance criterion for each scientifically sound batch-representative-sample-based in-process test should be appropriately** tighter than the acceptance criterion in the finished product batch-acceptance specification **unless the process steps subsequent to said in-process test cannot adversely affect the uniformity of the finished product. In such cases, the acceptance criterion for the in-process test can be identical to the acceptance criterion for the finished product specification when the subsequent steps do not affect batch uniformity. When subsequent in-process steps are known to improve batch uniformity, the acceptance criterion for the current phase should be appropriately wider than the acceptance criterion in the finished product specification."**	A specification limit depends on the precision associated with the reported test result. With some analytical procedures, the precision will depend on sample size or the number of samples used to obtain the reportable result. Sound science and the **CGMP** regulations require the setting of ***batch acceptance specifications*** (and not sample acceptance specifications) based on the testing of sufficient *batch-representative samples* that the result values obtained can validly be used to estimate the *uniformity of the batch* for the variable (e.g., active content, active availability, pH, clarity) being evaluated (not the range of sample values found for the samples tested). The requirements for establishing *scientifically sound* and *appropriate sampling* of appropriately sized (with respect to amount and number) *batch-representative samples* from in-process materials and the drug product, *testing* of *batch-representative numbers of unit-dose* (or smaller samples), and *batch acceptance specifications* (not sample specifications) that include statistical quality control (SQC) criteria (**21 CFR 211.165(d)**). This is the case because **CGMP** controls are required for the ***batch*** NOT for just the tested batch-representative *samples* thereof. Properly addressing the issues of *scientifically sound* and *appropriate sampling size*, the *sampling plan*, and the *number of batch-representative samples tested* is left to the individual firm. If the preceding is properly done, sufficient *batch-representative samples* will be tested in a manner that minimizes or overcomes the effect of precision associated with any individual test result. Assuring that the preceding direct and indirect **CGMP** requirements are met is the responsibility of the sponsor. 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 that the in-process limit should always be tighter without some qualification. This reviewer agrees; but only about the need for "some qualification." This reviewer's revisions provide the qualifiers that he knows are needed.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.D (P.3.4) (Cont.)	947-950 (Continued)		**(Reviewer's justification, Continued)** We feel that the word 'criterion' needs to be better explained. "Criterion," the singular of "criteria," means, "*any established rule (specification) by which an accept/reject decision can be made.*" This reviewer offers the preceding definition for inclusion in the Glossary to satisfy the commenters' stated need.
V.D (P.3.4)	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. This reviewer agrees provided the text "... justification for why it isn't ..." is changed to "... justification for why it **should not be the same or tighter ...**"	No rationale was provided.
E. Process Valid. And or Evaluat'n (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. This reviewer disagrees and suggests the following; "Validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug product, packaging components) should be submitted in this section of the application. When applicable, validation information should be provided for processes used to control adventitious agents. **Where appropriate,** the description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical tests used in the manufacturing process. However, submission of other manufacturing process validation information in the application is not necessary for most drug products.[25] **When provided,** this information should be included in A.2.	This paragraph currently starts out implying that process validation should be provided, but then later states that it is only required for specific situations. When starting to read this paragraph in its current form, it can be initially misleading. The commenters' rationale misstates what the paragraph states. This is the case because the text states conditions that: a) do require the submission of validation documentation (sterilization processes); **b)** may require the submission of validation information (adventitious agents) or **c)** may require the submission of validation and/or evaluation information (critical steps and critical tests). It also states that submission of other manufacturing process validation information is not necessary and, *via Footnote 25*, "[25]All manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits under current good manufacturing practices (CGMP) regulations (21 CFR part 211)," reminds all that **a)** all manufacturing processes must be validated and **b)** the Agency currently chooses to review these validations during its on-site inspectional audits. As to the commenters' request for prior examples, one of the lessons of history is that, *based on the problems found*, regulatory Agencies change their expectations of the industry that they regulate.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI (P.4)	981-986	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 listed under P.4 with no detailed information provided in P.4.1 through P.4.4. In any other circumstance, information should be included in P.4.1 through P.4.4 of the application. The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application." This reviewer disagrees and suggests that the draft text be incorporated into the guidance with the revisions proposed by this reviewer. This reviewer's rebuttals to the commenters' remarks and rationale statements can be found on this and the next three (3) pages. Thus, the guidance text should remain: "• Compendial-Non-novel Excipients:[26] When a compendial excipient is tested according to the monograph **tests and specifications** 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 listed under P.4 with no detailed information provided in P.4.1 through P.4.4 **other than the verification of the procedure's fitness in P.4.3.** . In any other circumstance, information should be included in P.4.1 through P.4.4 of the application. The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application."	The first proposed revision, "standard" to "**tests and specifications**," is designed to spell out what is being requested because the term, "monograph standard," is **a)** not defined and **b)** not generally understood in the industry.' The second, a proposed addition, is designed to align the reporting request to include the required verification for compendial test procedures. --- This section implies that if the applicant does not perform full testing on each batch of compendial excipient received, then the detailed information must be provided in sections P.4.1 through P.4.4. PhRMA does not believe that 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. ***Contrary to the commenters' remarks*, the current text simply and rightly states the conditions under which the sponsor can list the compendial references to the ingredient testing it is proposing without certain additional information.** Deleting the second condition would subvert the intent of this text – to insure that Agency reviewers will get detailed information in P.4.1 through P.4.4 whenever the applicant does not perform full testing – regardless of what testing the supplier may or the sponsor may perform. Thus, the commenters' first observation is not correct. *All that one can be properly infer from the text* is that some additional information will be needed – not that "all" will be needed. Moreover, whatever that information is, the extra information required is information that the firm is required to have to comply with **21 CFR 211** (the drug product **CGMP**). --- 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. Again, contrary to the commenters' statement, all that one should infer from the text cited is that properly *some additional information* will be needed in P.4.1 through P.4.4.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI (P.4) (Cont.)	981-986 (Continued)		Rationale / Justification, continued 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 compendial requirements. Contrary to the commenters' assertion, there is no such conflict. This is the case because the text cited is for the manufacturer releasing the compendial component and, since it permits the component maker not to do any compendial tests and, provided it is manufactured under some GMP, release the component as a **USP** component. In this instance, the commenters have: **a)** taken what the **USP General Notices** say out of context and **b)** misquoted it. In context, the **USP**, *discussing tests for the **RELEASE** of a compendial item into commerce **by the manufacturer thereof***, states: "However, it is not to be inferred that the application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards **before the batch is released for distribution. Data derived from *process validation* studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch.**" Thus, this reviewer fails to see how the **USP**'s guidance to the compendial item's manufacturer applies in this instance other than to point out that the excipient manufacturer may not be performing any compendial tests. Little wonder the Agency is concerned. Component supplier "A," operating under theirow n GMP, can establish that its controls and in-process tests ensure that the company's excipient product does comply with the **USP** and then release each batch as Component XYZ, **USP** without doing **one USP** test on that batch. To get **USP** testing on batches, this reviewer often had to include **USP** testing as a requirement in the purchase agreement and pay the additional costs because many ingredient suppliers do NOT routinely test each batch specifically for **USP** compliance – they use their own in-house controls which, for ISO suppliers, are superior for controlling the quality of the pharmaceutical-grade components they sell.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI (P.4) (Cont.)	981-986 (Continued)		Rationale / Justification (continued) Additionally, 21 CFR 211 Subpart E also allows the sponsor the ability to accept via COA, provided qualification has occurred. The commenters' statement is not correct. Factually, by omitting the requirement for "at least one specific identity test" (NOT an **Identification** test but a ***specific identity test***), the commenters misconstrue **21 CFR 211 Subpart E** in a manner that is critical to the understanding of what is required. Correctly, **21 CFR 211.84(d)(2)** states (emphases added): "... In lieu of such testing by the manufacturer, 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 analyses through appropriate validation *of the supplier's test results* at appropriate intervals." The reason that the phrase "specific identity" is crucial is that most of the **USP monograph**'s **IDENTIFICATION** tests are, *as written*, neither *specific* nor *identity tests* (in analytical testing, a specific test has to differentiate the material being tested from *all other similar* and dissimilar *materials* – a requirement that few tests meet and a requirement that the **USP IDENTIFICATION** tests rarely meet). In human terms, a *specific identity test* is like a test of your DNA; it identifies you from among all others except you, your identical twins, and your clones. *Identification tests* simply confirm one of your attributes – that you are male or female, or have blue or brown eyes or a blood type of O or AB.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI (P.4) (Cont.)	981-986 (Continued)		Rationale / Justification (continued) It is un reasonable to require the pharmaceutical manufacturer to commit to fully test every excipient lot at this point in the filing. Nothing requires the sponsor to commit to full testing on every excipient lot at any point prior to, in the filing, or thereafter. The choice is the sponsor's. Ifth e applicant decides that it needs to partition the testing between itself and the manufacturer of the excipient, or that it must do additional testing that is not in the compendium, *as often the case*, then the applicant needs to provide the requested information (P.4.1 through P.4.4). By providing this information, the applicant provides documented evidence of what it is doing and the values it is observing. In doing so, the applicant assists the application reviewers in determining whether or not the materials being used are adequately controlled in a manner that is **CGMP** compliant and ensures that the drug product will meet its specifications. --- The testing program is covered appropriately by the manufacturer's GMP program. First, this remark, if true, implies that such manufacturers are not operating incompliance with **CGMP** and their applications should not be approved – a GMP program is not defined for a drug or drug product manufacturer. Second, having a truly **CGMP**-compliant component-testing program does not preclude the Agency from asking for proof thereof – after all, by statute, all drug-product components are themselves drugs. --- Qualified Supplier" and other programs are entirely consistent with regulations and not the subject of the NDA. First, any data or information that is required to demonstrate compliance with any aspect of **CGMP** can be requested by the Agency in an application (ANDA and NDA). Second, in this reviewer's extensive experience, many firms seem to have "Quality Supplier" and related programs that do not test ***at least one specific identity test*** as required by **21 CFR 211.84(d)(2)** and therefore are NOT "entirely consistent with regulations."

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI (P.4)	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. Since American English is this reviewer's native tongue, it is clear that the request, as written, intends to ask for information in the format: "Excipient 1 (P.4,**US P** partial testing) P.4.1 Specifications **USP** Specifications 1, 3,5 and 7 In-house, in lieu of **USP**, 2, 4, and 6 from supplier's COA In-house, non-**USP** spec 8 and 9 P.4.2 Procedures. **USP** Procedures 1, 3, 5, and 7 In-house, in lieu of **USP**, 2, 4, and 6 from supplier, In-house non-**USP** procedure for 8 and 9 P.4.3 Validation Verification of **USP** procedures 1, 3, 5, and 7 In-house validation of supplier's procedures 2, 4, and 6 and verification of their results. In-house validations of procedures 8 & 9 P.4.4 Justifications In **USP** & not modified – 1, 3, 5,and 7. Copies of supplier's justification with Confirmatory testing for 2, 4 and 6 Full justification packages for tests 8 and 9 Excipient 2 (P4, **SUP** full testing) **SUP** Test name with confirmatory report establishing suitability for use in the sponsor's lab P.4.1 – P.4.4 – **See SUP** Excipient 3 ..."	No rationale provided. Based on this reviewers reading, the intent of the text is clear. However, because this text is guidance and not regulation, an applicant is free to use alternatives, provide the applicant's alternative satisfy the underlying regulatory requirements. While this reviewer finds that the commenters' last remark out of place here, this reviewer has attempted to provide an implicit listing as to what would seem to be needed in the "partial **USP**" and "full **USP**" cases as an aid to the commenters and perhaps as the basis for a tabular example in the CMC guidance.
VI (P.4)	993-994	It should be "IV.A.2"instead of "IV.B.2" This reviewer concurs.	Incorrect section is referred
VI (P.4)	1003	Please clarify why the patch should be different from drug products Apparently the reader that drafted this comment did not carefully read the text. The text addresses "**information on the components of ... the patch itself.**"	No rationale provided. The commenters apparently misread the text. Suggest diagramming sentence, as this reviewer does, whenever an apparent *disconnect or error* is found in text like: "**For example, information on the components of a *transdermal patch drug delivery system and the patch itself* should be included in P.4.1 through P.4.4.**"

Section	Guidance Line	Comment / Observation	Rationale / Justification
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.4.2 through P.4.4" on lines 983-984 conflicts with the statement in 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." Provided the revisions proposed by this reviewer are incorporated into the guidance text (**see the start of Row "981-986"**), this reviewer finds no conflict. Moreover, even without this reviewer's proposed revisions, there is no real conflict between **Lines 981** through **986**, governing "Compendial-Non-novel Excipients" and the text in **Lines 1008** through **1009** addressing "Specifications (P.4.1).	Clarity The commenters have apparently confused the phrase "**no detailed information**" with the phrase "no information." To meet the CMC guidance's requests in **Lines 1008-1009** for a "compendial-non-novel" excipient all that the applicant need do under P.4.1 is to state, "Specifications: **USP**," for that excipient (although the guidance does not prevent the applicant from doing more should they so choose).

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1)	1022-1024 and footnote 27	Delete the requirement to identify the 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). With the revision of the text proposed to align it with the requirements of **21 CFR 211.84(d)(2)**, this reviewer knowsth at this footnote should be included without the commenters' proposed deletions and would therefore propose the following text be adopted in the final CMC guidance: "[27] The drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)). The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate the **test or tests used to establish the specific identity of the excipient and the other** tests that will be performed once the reliability of the supplier's **test** results has been established in accordance with current good manufacturing practices."	Reviewer's Justification All that is needed is to request the applicant to clearly specify which test or tests establish the specific identity of the excipient as this must be done in any instance where a manufacturer elects to pursue the "accept COA" option for component acceptance. Further, the second change is to align the text of the footnote with that of the controlling **CGMP** regulation. Commenters' Rationale & Reviewer's Responses Thereto It isn't always known at the time of submission which tests the manufacturer will eventually accept on the vendor COA versus those performed by the manufacturer. At the time of submission of an NDA, the drug product manufacturer may have only limited experience with some excipients. This is especially true when new excipients or new suppliers of the excipients are used by the drug product manufacturer, and thus having only limited history of reliability. The implementation of a reduced testing program by the drug product manufacturer would likely occur well after the submission of the NDA. 1. The applicable **CGMP** requires the drug product manufacturer to have established the firm's specifications, standards, sampling plans, test procedures, and other laboratory control mechanisms before engaging in the manufacture of any drug product for introduction into commerce (**21 CFR 211.160(a).** Moreover, to be incompliance with the requirements of the **FDC Act**'s **CGMP** strictures, set forth in **Section 501(a)(2)(B)** of the act, the applicant must submit an application that demonstrates that the processes and control and drug products are in conformance with **CGMP**. Since a firm cannot know what its scientifically sound and appropriate specifications, sampling plans and test procedures are for a material unless it knows which tests it will be performing on that material, it is required for the manufacturer to know, at the time of submission, which tests it will perform. Therefore, a **CGMP**-complaint application cannot be submitted until the inspection plans that the firm proposes to use have been: **a)** established and **b)** approved by the applicant's quality control unit.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1) (Cont.)	1022-1024 and footnote 27 (Continued)		Rationale / Justification (continued) 2. Based on **Point 1**, while the manufacturer's experience may be limited, **CGMP** requires it to be sufficient to establish "**scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that**" each component conforms "**to appropriate standards of identity, strength, quality, and purity**" (**21 CFR 211.160(b)**). To be CGMP compliant, the applicant must have these before submitting an application or the application is violative (does not conform to the **FDC Act**'s expectations for **CGMP**). 3. Moreover, for the example given, the manufacturer's inspection plans would simply be required to be material source specific or hierarchical (have ***scientifically sound***: **a)** defined criteria for various levels of inspection **and b)** switching rules governing the progression from level to level – not such a big deal really. *In fact, a quality proactive company understands the utility of such plans and would probably have such for all control areas (incoming, in-process, release, and post release).* 4. To address the issue of reduced plans at later points, the firm need only submit a valid hierarchical plan like that discussed in **Point 3** – in a single submission. 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, provided that the manufacturer establishes the reliability of the suppliers analysis through appropriate validation of the supplier's test results at appropriate intervals." First, since, as the commenters seem to recognize, reliability of vendor testing is a **CGMP** issue, the Agency has the inspectional authority to address this issue as it sees fit. Thus, the Agency's request that this information be submitted is a proper request. Moreover, given today's FDA structure, reviewing this information in the application rather than by audit is, if the information is provided, likely to shorten the review period Based on the preceding, the text should be retained.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1) (Cont.)	1022-1024 and footnote 27 (Continued)		Rationale / Justification (continued) 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 This reviewer sees obvious reasons that the application should delineate who does what, the Agency needs to know where to send its staff to inspect and what they need to evaluate. Providing the delineation requested does that. Moreover, the commenters' statement concerning sNDAs (and by inference sANDAs) has nothing to do with what is requested and again points to the need for the Agency to know where each test will be performed – to ensure that the required supplements are filed in cases where the supplier deletes a test and the manufacturer does not add that test. Moreover, contrary to what the commenters allege, identifying who does what is "consistent with a risk-based approach." This is the case because the first precept to risk-based approaches is that the risks **must be identified**. Thus, if nothing else, noting the entity doing the test (supplier's in-house lab, manufacturer's in-house lab, supplier's contract lab, or manufacturer's contract lab or other lab) identifies the risk sources. Based on all of the preceding, the commenters' proposal should be rejected.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1)	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]." This reviewer disagrees. The footnote is properly placed. However, the text of the following sentence should be changed to, "At a minimum, the drug product manufacturer must perform **at least one specific identity** test (21 CFR 211.84(d)(**2**)."	Clarification Moving the footnote does nothing to clarify the guidance. Failing to correct the guidance fails to state the true minimum requirement. This is the case because, based on **21 CFR 211.84(d)(2)**, **21 CFR 211.84(d)(1)** is only the first part of what the manufacturer is required to do when the manufacturer does full testing. *In all other cases*, the manufacturer is required to comply with **21 CFR 211.84(d)(2)**. Moreover, the guidance's "**an appropriate identification test**" is not the same as the **CGMP** regulations' true requirement for the minimum that a manufacturer can do on representative samples from each shipment of each lot, "**at least one specific identity test.**" The reason that the words "**specific**" and "**identity**" are crucial is that most of the **USP monograph**'s **IDENTIFICATION** tests are, *as written*, neither *specific* nor *identity tests* (in analytical testing, a specific test has to differentiate the material being tested from *all other similar* and dissimilar *materials* – a requirement that few tests meet and a requirement that the **USP IDENTIFICATION** tests rarely meet). This reviewer emphasizes the clear difference between "identity" and "identification" by paraphrasing the preceding simple illustration. "In human terms, a *specific identity test* is like your DNA; it identifies you from among all others except you, your identical twins, and your clones. *An identification test* simply confirms one of your attributes – that you are male; or have brown eyes; or have a blood type of AB."
		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 ..." This reviewer disagrees ➔	"Clarification" The commenters' clause is at odds with one of the fundamental requirements of **CGMP** – the drug product manufacturer is responsible for the safety, quality, strength and purity of all the components, thus the manufacturer should establish that the supplier's COA results are valid whether or not they are used. *Without finding the supplier's COA results to be reliable*, how could a firm choose that supplier of the component and still assert that they are in compliance with either **CGMP** or sound business practice?
		Delete "However the specification should indicate the tests that will be performed once the reliability of the supplier's results has been established ..." This reviewer again objects to the proposed deletions for the reasons stated in the previous discussions.	

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1)	1038-1041	We request a definition of the term "official compendial monograph." We propose some latitude should be provided going beyond the USP to cite other recognized compendia such as EP and JP [spell out at least once the meaning of EP and JP].	No rationale was provided other than that implicit in the "Comment" column. By statute (**21 U.S.C. 321(j)**, the term "official compendium is clearly defined. Based on this, the term "official compendial monograph" must be defined as "any currently official monograph in an official compendium;" and this reviewer recommends that this definition be added to the Glossary to clarity the term. Should the Agency wish to "**spell out at least once the meaning of ...**", then this reviewer would suggest adding the following sentences after the definition of compendial monograph: "No pharmacopeia, or portion thereof, other than those that are recognized by the FDC Act as an "official compendium" are, *for the purposes of this guidance*, a compendium or, *in the case of a portion thereof*, compendial." Thus, all uses of the term compendium or compendial pertain to an official compendium because these are defined by statute."
		Otherwise, if the material in PhEur, 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. This reviewer, seeing the value in ensuring that the components used to manufacture a drug product are compendial, disagrees. →	The **USP *General Notices*** require *compendial drug products* to be made from *compendial components*. Thus, *if a manufacturer wants to continue legally selling the approved drug product in the United States once there is an official **USP** monograph for it*, they must either: **a.** ***Use compendial components*** in the drug product's manufacturer **or** **b.** ***Label said drug product*** in a manner that clearly indicates said drug product is ***NOT USP*** Therefore, unless the manufacturer finds: **a)** there is no value in labeling their drug product "**USP**," or **b)** the costs of doing so outweigh that value, they should ensure that the components they use are compendial. Rather than wasting time carping about the "value added for the extra testing ...", this reviewer knows that the commenters need only use supplier's who provide *compendial components*.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1)	1038-1041 1038 – 1041 Footnotes 10,20 and 26	"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 This reviewer agrees, finds that this guidance *inappropriately* uses the word "compendium" in only two instances in this draft (here and in **Line 1265**) and would recommend the following revisions: For **Lines 1038** through**1041**, revise text to: **"If the specification for an excipient is based on a pharmacopeia or FDA-recognized source other than an official compendium, the excipient should still conform to the official monograph in an official compendium when there is such a monograph."** For **Lines 1264** through **1265**, revise the text to: **"English-language translations of ~~Analytical~~ analytical procedures from any other published source (e.g., another country's ~~compendium~~ pharmacopeia, scientific journal) should be provided."**	Justification for reviewer's observations. In FDA guidance, the use of the words "compendium," "compendia," and "compendial" should only be used and/or taken to mean "official compendium," "official compendia," and "official compendial" so that the Agency's usage will comply with the FDC Act's statutory definition of "official compendium." When this is done, much of the confusion introduced by other use of these words is removed. Similarly, to remove any confusion, the word "monograph" should be taken ONLY to mean and encompass the definition of the term "official monograph" and, unless obviously redundant, the phrase "official monograph" should be used in this guidance's text. Finally, just as the term "official compendium" has been defined in this guidance, the term "official monograph" should also be defined – preferably in the Glossary. Were these suggestions to be adopted, the guidance should be clear to all those knowledgeable individuals dealing with any facet of the **CGMP** and filing regulations appertaining to the CMC section of an application (ANDA or NDA). Rationale / Justification What compendia are not official as it relates to this document? Provide the word "compendia" is properly used, the answer is NONE (see Reviewer's previous remarks. 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 Pharmacopeia. First, though published together, the **USP** and the **NF** are separate compendia. Ignoring that point, this reviewer agrees and has already recommended the appropriate revision of **Footnote 10 (see Row "302")** to: [10] The statute (**FDC Act** at **21 U.S.C. 321(j)**) defines the term "official compendium" as follows: **"The term 'official compendium' means the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.**

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1) (Cont.)	1038-1041 1038 – 1041 Footnotes 10,20 and 26 (Continued)		Rationale / Justification (Continued) 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 the other compendia but not in the USP-NF. First, because of the statutory constraints imposed by **21 U.S.C. Title 9**, this reviewer cannot agree with the reviewer's remark concerning the "status" of the pharmacopeias cited or that of any other such. This is the case because legally they have no regulatory status except that, to the extent recognized by the FDA, a **CGMP**-regulated firm may reference their test procedures (***but not their specifications***) in reporting the history of the development of the test procedures used by that manufacturer, processor, packer or holder of a drug product. This reviewer suggests that the commenters carefully consider these realities and the reviewer's previous remarks to this "row" and the previous related "rows" in the commenters' "**SCORECARD**" table. Conforming to the "monograph" has a different meaning than conforming to the "compendia", e.g., meeting compendia means complying with the General Chapters and applicable GMPs as well as meeting the requirements of the monograph. At least with respect to the **USP** and the **NF**, this reviewer must disagree because the commenters' statement, as written, is not true. Factually asserting conformance to an *official monograph* is asserting conformance to the *official compendium*. This reviewer would recommend that the commenters carefully read the **USP *General Notices***. What is true is that a firm's assertion that a component conforms to the ***specifications*** in an official monograph (as, in reality, many suppliers' COAs do) is not an assertion of conformance to the official monograph. Also, the legally recognized "official compendia" for the FDA are the USP-NF and the Homeopahtic Pharmacopeia as per the Federal Food, Drug, and Cosmetic Act. As written, the commenters' statement is not quite correct (**see Reviewer's** proposed **Footnote 10**).

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.A (P.4.1)	1044	Replace "EP" with "Ph.Eur." This reviewer disagrees and, instead, proposes a more general revision of the text in **Lines 1043** through **1045**: "Certain *General Chapters* in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of ~~the *European Pharmacopoeia* (EP) and the *Japanese Pharmacopoeia* (JP)~~ **other pharmacopeias**. Likewise, this reviewer proposes to change **Lines 1062** though **1066** "When analytical procedures from the current revision of an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods, analytical procedures from ~~EP or JP~~ other FDA-recognized **pharmacopeias** that are interchangeable with a USP *General Chapter*) are used, they should be verified to be suitable under actual conditions of use." Finally, this reviewer proposes to change **Footnote 30** (**Drft. Gdnc.**, page 35) to [30] See section ~~VI.B~~ **VI.A** for guidance on USP *General Chapters* that are interchangeable with ~~EP or JP~~ **the corresponding** analytical procedures **found in those pharmacopeias harmonized with the USP or the NF.**"	Use official abbreviation Alternatives are proposed for the three instances found in the draft text. These alternatives are proposed to reduce the need for minor technical changes to this guidance after it is issued that are caused by changes initiated by agencies outside of the jurisdiction of the FDA as is the case here. Moreover, in the future other pharmacopeias (besides the ***European Pharmacopeia*** ["**EP**," currently abbreviated as "**Ph.Eur**". or "**Ph. Eur.**" or the ***Japanese Pharmacopeia*** ["**JP**"]) may be harmonized with the **USP** and the **NF** or, *as in the case of the* ***British Pharmacopeia*** *("**BP**")*, be recognized by the **FDA** as a standard reference. Further, the changes proposed **a)** properly address the underlying concern of the commenters, referencing accuracy, without **b)** incurring the need of continual revision precipitated by changes by agencies outside of the **FDA**'s control. Lastly, the correct citation to harmonized chapters is **VI. A.** (**See Lines 1043 – 1046.**)
VI.A (P.4.1)	1046	Replace "result obtained from USP" with "decision will be based on science." This reviewer cannot agree with the change proposed because to do so would be to be engaged in the subversion of the regulatory process. However, the text in **Lines 1045** and **1046** needs to be modified slightly: "However, where a difference appears, or in the event of dispute, the result obtained from the ~~USP~~ procedure **in the USP, or, where such exist, any other official compendium** is conclusive. --- "If the USP is not used, an explanation should be provided as to why USP is not used." With respect to dispute resolution, the standards, tests and specs in an "**official compendium**" must be used!	Should be verification as to the currentness of USP. Since the official compendia are recognized by statute as the *sole legal arbitrator* of all disputes involving any drug or component of a drug *in commerce*, any binding requirements (standards, tests and specifications) that these compendia establish for a material are the sole arbitrators in disputes. Thus, all decisions are required to be based on the official compendia and the text should either remain as it is or be changed as this reviewer suggests. --- Additionally, product specific quality may require use of the "non-USP" grade of material if it is more suitable. *If true and the product is an NDA product,* submi and work to add the grade to **USP** or **NF**. *If true and ANDA product,* work to change the **USI** or **NF** *before submitting* CMC section.

Section	Guidance Line	Comment / Observation	Rationale / Justification
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 to this list. This reviewer supports the commenters' request for the **FDA** to provide a reference to a "list" and would suggest that the basis of the "list" be the pertinent parts of the CDRH list mandated by FDAMA. Further, in the interests of commonality across jurisdictions, the recognized ISO documents, where they exist should be listed first (with the corresponding American National standards, where they exist, listed in parentheses "( )" after the primary reference.	No rationale was provided. Given the demonstrated apparent lack of knowledge in the industry and the Agency concerning the available reference standard sources for test procedure (scientific journals and methods publications that only publish procedures after peer review and with formal mechanisms to ensure that post-publication criticisms are published and answered) as well as the available reference procedures for the sampling of discrete populations for testing for variable properties), this reviewer would suggest an annually updated "**FDA** recognized" list divided in to categories that match those in **21 CFR 211.160(b):** **Recognized Sources** 1. **Specifications** [Post-release In-commerce Basis Set (**USP, NF and HP-US**), and, for In-process and Acceptance, Development (reference statistics texts that address) and In-Use Suitability Verification (reference texts that address)], 2. **Sources for Reference Standard Materials** [Primary (e.g., USP, NIST, Aldrich, Baker, Sigma) and Secondary (e.g., Aldrich, Baker, Sigma, Fisher,] 3. **"Population [*Batch and Lot*]"Representative Sample" Sampling Plans** [for Non-Discrete Materials (reference texts that address), and for Discrete Entity (for 95 % confidence level, ISO standards and ISO-equivalent ANS standards and, for other confidence levels reference statistical texts], and 4. **Testing Procedures** [Quantitative, Semi Quantitative {Including Limit}, and Qualitative (AOAC International Book o Methods, USP, NF, and other recognized pharmacopeias and journals]).
VI.B (P.4.2.B)	1055	The document cites the AOAC International Book of Methods as a FDA-recognized standard reference. Microbiological methods may also be found in APhA Standards, e.g., Standard Method 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. While, in principle, this reviewer agrees, the Agency's ability to unilaterally recognize such is limited.	Acceptable alternate microbiological methods may be used. In cases where the procedures can be used fo post-release purposes, the Agency needs the a least one of the three (3) official compendia t recognize it before the **FDA** can do so. Therefore, this reviewer would suggest tha the industry set up a joint task force (**FDA**, **USI** and industry) to address this area, and t purpose the adding of general language to th current language in the CMC draft guidance t enable the addition and deletion of such withou the need to change the guidance.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.C (P.4.3)	1063	Revise to read as follows: Analytical procedures for excipients should be validated or verified as appropriate." For clearly stated reasons, this → reviewer disagrees and recommends that the text be modified to reflect the lesser level of validation allowed for compendial excipients: "All analytical procedures for excipients should be validated **or, when they are unmodified analytical procedures from an FDA-recognized source, should have their suitability for use verified under the actual conditions of use.**"	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 this need not be validated. Unfortunately, the commenters' beliefs provide little in the way of factual rationale. Second, in the drug CGMP, **21 CFR 211.194(a)(2)** states: "... **The suitability of all testing methods used shall be verified under actual conditions of use.**" Since this has been a CGMP requirement since 1979, this reviewer has a hard time "believing" that the commenters do not know that this is a minimum requirement for **all** analytical procedures. The text clearly indicates that, ***if used without modification***, compendial methods and methods from any other FDA-recognized source need only be "**verified to be suitable under actual conditions of use.**" Given the **CGMP** requirement, the language could, if such were deemed necessary, be changed to read " **All analytical procedures for excipients should be validated** or, ..., verified under actual conditions of use." Thus, in the context of **21 CFR 211.194(a)(2)**, having "**verified**" such an excipient method "**to be suitable under actual conditions of use**" results in a "**validated**" analytical procedure for that excipient. Therefore, in context, there is no need to add that phrase to the text as it is scientifically, logically and regulationally correct as written. However, to satisfy the need for some "flexibility" expressed by this and other commenters, this reviewer reluctantly supports adding to the draft language.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.C (P.4.3) VII.C (P.5.3)	1066-1072, and 1273-1274	Clarify the statement to exclude the requirements 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 *(reviewer inserted original text and marked it to show changes to show what and how text was changed)*: "**Validation information should be submitted if ~~there are~~** for additional test(s) required by **special circumstances** that are not covered in or performed as described in an official compendium. **For example, ~~submission of validation information for an excipient can be appropriate~~** 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 or is not assessed as part of the drug product testing.**" This reviewer disagrees and, for the reasons presented on this page and the following page, knows that the language in this draft guidance should be retained.	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. All **USP General Chapters** beyond **<1000>** are non-binding guidance chapters Per 21 CFR 211.194~~(a)(2)~~ "~~(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:~~ ~~(2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested.~~ (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)~~. The suitability of all testing methods used shall be verified under actual conditions of use.~~" *As almost all who read this section of **21 CFR 211.194** do,* the commenters have removed a parenthetical remark referring to the "**the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested**" and made it into something that it is not, an "exemption" from the requirement to validate all methods used, at some level. Obviously, unless a firm developed an "FDA-recognized method," that firm cannot reference (point to) the location of the data – iti s out of their control. Thus, the regulation, *recognizing that reality,* permits simply citing the method and the reference to it in such cases PROVIDED the method is used without modification. Moreover, *to insure that all methods are validated to some degree,* the regulation continues with, "**The suitability of all testing methods used shall be verified under actual conditions of use.**" Thus, all testing methods (analytical test procedures and other test methods) must have their suitability verified under actualco nditions of use. Factually, **a)** successfully performing the preceding validates the method **and b)**, *since actual conditions change,* this verification must be done each time the test method is used.

Section	Guidance Line	Comment / Observation	Rationale / Justification
(Cont.) VI.C (P.4.3) **VII.C (P.5.3)**	(Continued) 1066-1072, and 1273-1274	Comment / Observation (Continued) 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 experimental data, for the analytical procedures used for testing the drug product should be provided. This reviewer disagrees and, for the reasons presented on this page and the preceding page, knows that the language in this draft guidance should be retained. In conclusion, this reviewer's experience and training has provided ample evidence that **a)** the validation (as defined in this guidance to include verification of the method under actual conditions of use for compendial methods [**Lines 1062 – 1066**]) is needed and **b)** the Agency's requests [**Lines 1062 – 1066**, and **1273-1274**] are valid and place the emphasis where it should on asking the applicant to submit proof that the validity of the firm's process controls for "critical control points" has been established – a predicate for risk-based decision making (the risks must be identified).	Rationale/Justification (Continued) Reading the commenters suggested changes, this reviewer understands that the commenters want to: **a)** not report any validation of test methods and **b)** limit validation to tests not in an official compendium. However, the **CGMP** regulations do not permit "**b)**" and to the extent that all test procedures are required to be ***established*** (proven) and ***scientifically sound*** (**21 CFR 211.160**), all **CGMP**-compliant firms regulated by **21 CFR Parts 210** through **226** will know that test procedures must be validated and have done so. Moreover, **21 CFR 211.110(a)** states: "To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." What manufacturing process is more in need of monitoring and validating than the analytical test process? Isn't validating the analytical testing procedure as critical, or more, critical than many of the processing steps the procedure will be used to test the required samples? You would think that applicants would not be objecting to providing the requested information when the **CGMP** regulations clearly require the applicant to have that information – yet they have and are. The alternatives suggested in both the first and second instances are much less desirable because they would, if adopted, **a)** Result in the omission of important information for some *critical control points* – definitely an anti-quality position, **b)** Necessitate the Agency's expansion of its "PAI" activities, and **c)** Continue to delay approvals when significant deficiencies are found in one of the applicant's sites' compliance with **CGMP** because the test methods used are found to be: **i)** not properly validated or **ii)**, in some cases, not valid.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.C (P.4.3)	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." This reviewer disagrees and recommends leaving the draft text as it is, **"For compendial excipients, justification of the acceptance criteria for tests beyond those included in the monographs is recommended (e.g., particle size, flow properties, impurities)."** This recommendation is made for the reasons provided and the reality that any firm that does additional testing does so because of some requirement that directly or indirectly can affect product performance or the manufacturing process. No firm that this reviewer has encountered does, *as the proposed addition implies*, additional tests just to increase the test burden on their "incoming components" labs.	Clarification Since this document is guidance and since the statement made is a recommendation in guidance, this reviewer sees no need to reduce the clarity of the statement by adding verbiage that restricts a non-binding recommendation that is counter to **CGMP** which requires regulated firms to ***establish scientifically sound*** and *appropriate specifications* for all materials (**21 CFR 211.160**). This reviewer is at a loss how af irm can establish (prove) that a specification is ***scientifically sound*** and ***appropriate*** for any component intended for a specific use **unless** that firm provides a science-based justification of the specifications set by the regulated firm. Based on this reviewer's decades of experience in this regard, mosta ll component suppliers of excipients do, can or, for a price, are willing to provide any grade of excipient (*within the envelope of what can be manufactured in their facilities*) that a regulated firm may require for a given drug-product manufacturing process. Similarly, obtaining *reproducible* blending of dry ingredients is critically dependent on the physiochemical properties of the excipients and their interactions with each other and the active or actives. Based on the preceding, the identification and rigorous control of those properties of the components that are critical to the reproducible production of the drug product even, in some cases, for liquids (solutions and syrups). Thus, a quality-proactive, regulated firm will establish the specifications of the critical ingredient variable factors within the ranges provided in an official compendium or, if the test is not in the compendium or the component is not compendial, based on specifications from other sources. For non-significant variables, the firms may elect to accept the compendial specification provided they justify (prove that choice has no adverse impact on) the specifications so designated. [For example, the pH of a dry solid excipient is of less concern to a firm that manufactures tablets by processes that do not involve steps using liquids ("wet granulation") than it is for a firm that uses water- or alcohol- based granulation and granulation drying steps, and much less than that of a firm using that excipient to make liquids.]

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.C (P.4.3)	1081-1082	The justification of specifications for non-compendial excipients as recommended for drug substance should not be required for most non-compendial excipients. It is more appropriate for novel excipients. This reviewer knows that the preceding statement is at odds not only with the drug **CGMP** regulations set forth in **21 CFR Parts 210** through **226**, but also with the **Federal Food, Drug, and Cosmetic Act** which defines the components of a drug as a drug (**21 U.S.C. 321(g)**, "(g)(1) The term ``drug'' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). ..." at **21 U.S.C. 312(g)(1)(D)**).	Clarification Apparently, the commenters have failed to read the sections of the drug **CGMP** regulations governing the components especially those contained in **21 CFR 211.84** and **21 CFR 211.160(b)(2).** Since 1979, the legal regulations governing the manufacture of drug products have required all components (active and inactive) to be treated in the same manner. Moreover, the text in**Li nes 1081 – 1082** should be reviewed in their context (**Lines 1078 – 1087**): "Justifications for the proposed excipient specifications should be provided where appropriate. For compendial excipients, justification of the acceptance criteria for tests beyond those included in the monographs is recommended (e.g., particle size, flow properties, impurities). The specifications for noncompendial excipients should be justified as recommended for the drug substance (guidance will be provided in the discussion of section S.4.5 of the forthcoming drug substance guidance). The justification should be based on relevant development data (P.2.1.2), batch analyses (P.5.4, R.1.P), and any other relevant data such as data from drug product stability studies (P.8). The discussion in this section should unify, either by reference or in summary, data and information that are located in other sections of the application." Reviewing this paragraph, the first thing this reviewer notes is that such justifications are only requested where it is appropriate to do so ("Justifications for the proposed excipient specifications should be provided where appropriate." [with underlining added for emphasis]. For compendial excipients, the guidance simply requests a "justification of the acceptance criteria for tests beyond those included in the monographs." For noncompendial excipients, the guidance requests the "specifications for noncompendial excipients should be justified as recommended for the drug substance" which is their proper treatment because **by law** any component of a drug product, *including any excipient*, is a drug. Thus, though, by law and regulation, applicants are required to have the justifications of the specifications for all components, the guidance is only requesting that a limited set be provided in the CMC section of the application.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.D (P.4.4)	1089-1094	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. **[Current Guidance Cross-Reference: 21 CFR 211.84(d)(2) and ICH Q7A Section 7.31]** This reviewer sees at least two good reasons for requesting that the COA from the manufacturer of the excipient and the drug product manufacturer's test results from the same batch(es) used in the drug-product batch(es) described in the executed production record (R.1.P). Thus, this reviewer knows that the text should remain: "A certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4. The information should be for the materials used to produce the batch described in the executed production record (R.1.P)." --- 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 commenters' remark points to a continual misrepresentation of what is required by **21 CFR 211.84(d)(2)**. Factually, under CGMP, **Sec. 211.84(d)(2)** requires a firm to perform at least "**one specific identity**" test on ***representative samples from each shipment of each lot of each component*** **(21 CFR 211.160(b)(1)** and **21 CFR 211.84(b))**. As this reviewer has established, specific identity tests: **a)** Are not "ID" (identification) tests and **b)** *Except in rare cases*, are not any of one, or, for that matter, all the tests in the official compendial "excipient" monographs under "IDENTIFICATION" (or, for that matter, in any pharmacopeia).	Reviewer's Justification First, as written, this guidance will help ensure that the COAs submitted in an application are "ingredient manufacturer" COAs (what the regulations require) rather than, as is often the case, "supplier" COAs from intermediaries. Second, appropriately placing information that may be in other sections in P.4 (*not necessarily in the commenters' P.4.4*) will speed the application review process although, *because this document is guidance*, the applicant is free to appropriately provide a reference in P.4 to the appropriate portions of R.1.P. --- Rationale / Justification 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. This statement is not a rationale; it is the commenters' position. --- The request for both vendor COA results and drug product manufacturers results for components used in lots provided in the execution 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 production records and at a time after submission or approval of the application. Factually, this request is: **a)** not a requirement and **b)** does not encroach on any **CGMP** responsibility that an applicant has. This request is simply a request that the responsible party, the applicant, provide excipient information from the manufacturer of the excipient and the applying manufacturer of the proposedd rug product pursuant to the Agency's responsibility to ensure that firm's are **CGMP** compliant before approving their applications. Further, what **CGMP**-compliant firm would purchase components for the development of a new drug-product manufacturing process from a supplier without verifying that the component meets both the commercial (in commerce) and contractual specifications appertaining thereto?

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.D (P.4.4) (Cont.)	1089-1094 (Continued)		Rationale / Justification (continued) If it is necessary to determine whether appropriate quality systems are in place for control of vendors, this could be done during inspections. Because the Agency needs evidence in the application to establish that the filed production processes, including incoming component receipt, handling, and release, and the drug product controls meet all applicable CGMP requirements, the Agency's requesting this information in an application is just as appropriate as requesting that same information during an inspection. Therefore, this reviewer does not understand the import of the commenters' remark. Moreover, when the information requested is provided, the Agency reviewer can ascertain compliance without wasting valuable but limited inspection time having a compliance officer visit the site and, by searching through the site's records, find and gather the requested information. After all, the application reviewers, as any other Agency personnel involved in the application review and approval process, do have the responsibility to ensure that an application demonstrates that the applicants components, processes, controls, materials, drug products, and regulated systems are or, if operated as presented, will be fully **CGMP**-compliant.
VI.D (P.4.4) VI.D (P.5.4) XII.A.2 (R.1.P)	1092-1094, 1308-1309 and 1819-1821	In the statement, "Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate," change "as appropriate" to "where practical." This reviewer disagrees; the draft text should be retained.	It may be difficult to express all results numerically or qualitatively. If the proposed change were made then the sentence would mean: "Test results should be expressed numerically where practical or qualitatively (e.g., clear, colorless solution), where practical." Obviously, the first instance would permit the applicant not to report the analytical results obtained on the grounds that to do so is not practical. Therefore, the **"as appropriate"** language should be retained and the commenter's proposal in this regard should be rejected. (**See** next page for other commenters' remarks and this reviewer's remarks appertaining thereto.)

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.D (P.4.4) VI.D (P.5.4) XII.A.2 (R.1.P) (Cont.)	1092-1094, 1307-1309 and 1819- 1821 [Slight citing errors for the text in the (Continued)	Comment/**Observation** (Continued) Delete the next sentence which states: "Use of terms such as conforms or meets specifications is discouraged." Use of terms such as "conforms" or "meets specifications" should be appropriate to use as when it is clear what specification the test result has been assessed against. This reviewer does not understand, do the commenters want to use terms like "conforms" and meets specifications or don't they" If they do, all that needs to be done is to retain the sentence they propose to delete. Moreover, taking the commenters' at their word that it should be clear what specification the test result has been assessed against would suggest that text be added to reflect their concern. Thus, this reviewer would propose the following revision: "Use of terms such as *conforms* or *meets specifications* is discouraged **and, when these terms are used, the report containing them should include the detailed specification that the component tested conforms to or meets.**"	Rationale / Justification (continued) 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. While the preceding does represent the complexity of reporting a single result for an IDENTIFICATION test for Aluminum Stearate, apparently seeks to deliberately mislead the reader by casting the test cited as an **identity test** when, in fact, it is nothing of the sort. First of all, there are myriads of mixtures that would pass this identification test. To pass, all they need be is, for example, a mixture of the appropriate material and some other material that is related or, if unrelated, does not interfere with the test. For example, a 50:50 mixture of Aluminum Monostearate and Stearic Acid would pass this test as would a 50:50 mixture of this component with Sodium Chloride (salt). Therefore, this is an "Identification" test, it excludes materials that contain no or trace levels of Aluminum and those that are not salts of fatty acids that are oils at room temperature, but it does not identify the material tested as being Aluminum Monostearate. Moreover, the commenters' "Identity A" seems to be specious because, so this reviewer thinks, the **USP** text is: "**Identification–** **A:** ..." The later liberty with reality that the commenters seem to have taken confirms this reviewer's suspicion that the commenters have, in this instance, knowingly submitted a misleading comment. In these cases, the use of the terms "conforms" or "meets specifications" should be acceptable. Apparently the commenters do not understand the next sentence in the guidance text (**Lines 1093 – 1094**; **Lines 1308 – 1309**; and **Lines 1819-1821**), "Use of terms such as *conforms* or *meets specifications* is discouraged." As guidance it does not suggest that these terms should not be used but rather that their use should be restricted to cases where the alternative is truly untenable.

Section	Guidance Line	Comment / Observation	Rationale / Justification
~~1102~~ **VI.E (P.4,5)**	1102-1104	Revise to read as follows: "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." This reviewer disagrees with the revision of the current text, "**Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11),**" and would suggest, as the commenters did in their "**V.C.2**, 824, that this sentence be added at the beginning of this paragraph (**Lines 1100 – 1106**) with the minor modifications previously proposed by this reviewer: "If ruminant derived materials are used or manipulated in the same manufacturing equipment as the new product, a statement should be provided regarding **the** control measures (such as sourcing, manufacturing processing conditions, and the nature of the tissues) used to minimize the risk of TSE **contamination. Excipients of human or animal origin should be identified. The genus, species, country of origin, source (e.g., pancreas), and manufacturer or supplier should be clearly indicated. Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11). Guidance is available from FDA on *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use.***"	The commenters provided no rationale. The modifications suggested: **a)** improve the grammatical correctness and **b)** correct the "risk of" statement to reflect the risk being controlled, "TSE **contamination.**" However, recognizing the need for the certify (state) the true country of origin for these, this reviewer knows that this sentence should not be replaced here. Moreover, the reviewer's proposal is consistent with the commenters' proposal in **V.C.2**, 824. Finally, to the extent possible, the guidance provided should at least be consistent across a given guidance document promulgated under GGP by the **FDA**.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VI.F. (P.4.6)	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. This reviewer agrees that such may be useful but also notes that they may not be useful. Thus, until and unless, the commenters present a sound proposal that spells out the details, provides sound science that supports it, and establishes that it complies with both the requirements and the spirit of CGMP, this reviewer would recommend that comments such as this be ignored.	The commenters provided no rationale. This reviewer notes that almost anything may be useful – that is not a debatable or relevant issue. Until the commenters present much more that a "may be" statement, this reviewer would recommend ignoring such comments as they are, at best, tangential to this guidance document and the issuance thereof. Since guidance is, just that, guidance and not regulation and the applicant's have ready access to Agency to address any issues specific to a particular application, there is no compelling reason to consider the points alluded to, but not raised in a cogent manner, in this comment.
VI.F. (P.4.6)	1121	Please move the entire paragraph starting with "Additionally, full details of the manufacture ..." to Sec. IV.A.2 under novel excipients. This reviewer disagrees. ➔ However, this reviewer does recommend a revision to remove the reference to guidance that does not exist, as follows: "Additionally, full details of manufacture, characterization, and controls, with cross-references to supporting safety (nonclinical and/or clinical) data, should be provided. The information should provide the same level of detail as that provided for a drug substance, and according to the drug substance format **that is official at the time that the application is filed** ~~(guidance will be provided in the forthcoming drug substance guidance)~~. This detailed information should be provided in A.3 unless the information is provided in an appropriately referenced DMF."	Paragraph 1121 contains information more appropriate to be referenced in the Pharmaceutical Development Section. The information request is for the novel excipient that the drug-product manufacturer proposes to use and not for the development of which excipient to use. On that basis alone, the information requested should be placed where it is. Also the CTD specifically creates a section for "novel" excipients under which information key to such should be filed. Though most novel excipients will be chemicals and mixtures that exist and have extensive background data, the Agency is properly requesting that the applicant submit the detailed information as to how the particular source of the "novel" excipient manufactures it because, unlike non-novel excipients, the Agency does not, in general, have that information on file to review. Charged with ensuring public safety and with the requirement to treat excipients as drugs, the Agency should do no less than it is doing here. In cases, where the applicant has a different view, the applicant may pursue that course of action provided it is at least equivalent to the guidance offered and, *more important*, complies with the requirement minimums of **CGMP**.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.A (P.5.1)	Footnote 30 (p.32)	Change "VI.B" to "VI.A" The commenters are correct. However, the use of the word "Guideline" in their rationale is, at best, unfortunate – the document is being proposed as guidance and not, as this answer, implies, a guideline.	The information on interchangeable chapters is provided at the end of section VI.A. in the Guideline, not in section VI.B. The exact citation in the draft text of this guidance to the harmonized chapters would be **VI. A. (Lines 1043 – 1046)**.
VII.A (P.5.1)	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 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. Since what is proposed is consistent with the CTD format, this reviewer would suggest that the commenters' concerns be addressed by correcting their misimpression that, among other things, P.5.1 and P.5.2 could be viewed as the complete statement of all regulatory tests and methods.	The commenters provided no supporting rationale. Apparently, the purpose of this involved commentary is to attempt to have the Agency swallow the unsupported premise that "P.5.1 and P.5.2 can also be appropriately viewed as the complete statement of all regulatory tests and methods." Hopefully, the Agency will recognize this reality and address it as they see fit. In the mean time, this reviewer will recommend that this draft text be left as it is. This the case because nothing in this text prevents it from being described in both places or, where appropriate (when its use is contemplated as being ongoing), referencing the appropriate portion of P.8.3 in P.5.1 or P.5.2.
VII.A (P.5.1)	1149	Include definition for "sunset provision." This reviewer agrees.	Commenters provided no rationale. Terms that are used for which there are no statutory, regulatory, or other recognized Agency definition in related guidances should be defined in the Glossary of this guidance. Doing this should ensure terms are defined and that the definitions presented are consistent with the applicable statutes and regulations. However, no **CGMP**-required control should be allowed to be included in any sunset provision. What should be encouraged is the *scientifically sound* and *appropriate* use of hierarchical inspection plans with science-based level switching criteria for the switching among the scientifically sound levels defined in said inspection plans.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.A (P.5.1)	1162 1174 Table	The inclusion of release criteria should be an option not a US requirement. For the reasons stated, this reviewer not only disagrees and but also recognizes that this information is key to the application reviewers' ability to determine that the production process and the drug product comply with CGMP. This text should therefore be incorporated without change into the final CMC guidance. [**Note:** Since 1979, if a firm has operated in compliance with CGMP (*as the FDC Act requires*), they have had two specifications for their product, 1. **A statistically based specification** that complies with all the applicable requirements of **21 CFR 211.160, Sec. 211.165, Sec. 211.166**, and **211.167** including the specific requirements set forth in **21 CFR 211.160(b)(3) and 21 CFR 211.165(d)**, and 2. **A USP-based *post-release* lifetime specification** for articles in commerce.] Thus, the guidance's request is but another request for the firm to establish that its applications comply with **CGMP**. What is clear is that the **FDA**'s guidance is requesting that a firm provide proof of compliance with the batch-release requirements of drug **CGMP**. As the commenters' first rationale comment clearly indicates, nothing that a firm has <u>not</u> been required to comply with for more than two decades is being requested. Upon reflection, the commenters should have no problem with providing the **FDA** with proof that their applications comply with the legal strictures governing their **FDA**-approved or licensed operations and drugs in whatever setting the **FDA** requests it to be provided.	Release criteria are an internal cGMP issue and not an application 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 US requirement. At least the commenters recognize that release criteria are a CGMP issue. However, all CGMP issues are also application review issues contrary to the commenters' assertions. Moreover, the allusion to the European application approach is just a feeble attempt to distract the reader from what is requested and what a minimally CGMP-compliant drug manufacturer is supposed to do. Again, this reviewer would recommend that the commenter carefully read the CGMP requirements for drug product release set forth in **21 CFR 211.160**, **165**, and **167** and the **General Notices** section of the **USP** that clearly states the **USP**'s "in commerce" sampling plans are "not statistical sampling plans," its lifetime post-release specifications may, or may <u>not</u>, be appropriate for release, and each firm should develop appropriate release specifications. In doing so, the commenter should focus on the requirements of **21 CFR 211.165(d)**, "**Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.**" Since to comply with **21 CFR 211.165**, one must a valid statistical sampling plan and the **USP**'s sampling plans are <u>not</u> statistical sampling plans, the release specifications <u>cannot</u> validly be based on any aspect of the **USP**'s sampling plan. Thus, since 1979, the **CGMP** regulations have required release specifications that are scientifically sound and based on, among other things, ***statistical quality control*** (**SQC**) and the **FDC Act** has required, post-release compliance to the non-statistical **USP's** "*article in commerce complies when tested*" requirements.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.A	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). This reviewer agrees but notes that this is just a "repackaging" of the comment made in a table row labeled by the commenters in the "Guidance Line" column as "Footnote 30 (p.32)." Moreover, in that instance, the rationale, "The information on interchangeable chapters is provided at the end of section VI.A. in the Guideline, not in section VI.B." corrected the error, though their use of the word "Guideline" was unfortunate.	Clarification. The exact citation in the draft text of this guidance to the harmonized chapters would be **VI. A. (See Lines 1043 – 1046.)**
VII.A (P.5.1)	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. Contrary to the commenter's statement, detailed, **CGMP**-compliant batch release should be provided because they are crucial to establishing the requisite **CGMP** compliance of the drug product. This reviewer suggests that the commenters carefully read the relevant comments and the pertinent alternate "**Table 3**" example posted to this docket on 20 May 2003.	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. Contrary to what the commenter states, scientifically sound non-functional tests are of great value as in-process controls (accept/reject criteria) and most firms use them for tests such as appearance, dimension, imperfections, hardness, friability, dose weight or dose volume, deliverable volume, defects, and the like. Technically in-process core (IPC) weight testing on a batch representative set of cores should be an integral part of the critical controls for release of the cores for further processing. However, for most film coated tablet drug products, the final tablet weights should be included in the batch release controls. This is the case so that the specific content and the specific drug availability values may be assessed to conform the uniformity of the final blend that was formed into the dosage units. As was the case for the IPCs, a batch representative set is needed for each critical variable that is evaluated to determine (based on SQC) whether or not the batch (not just the samples tested) is acceptable for release. Further, the IPC example again brings up the question if the testing needs to be carried out in the Quality Unit. Since the CGMP regulations do not specify WHERE any tests must be conducted, this reviewer sees no such location issue.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.A (P.5.1)	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. While this reviewer agrees that a "reference is needed to indicate the identification threshold," this reviewer knows that this should be established on safety/toxicity basis and not any prescriptive number.	The commenters provided no rationale. *Since there are many known chemicals and elements that have ppm (< 0. 01 %) and, in a some cases, ppb (< 0.0001 %) limits*, it would not be *scientifically sound* or ethical for the Agency, or any other body charged with the responsibility for protecting the health and safety of those who consume drug products, to set, or purpose any prescriptive "non-risk-based" limit for any impurity. In the late 1970's, the EPA recognized the reality of the proceeding. This reviewer would only hope that the **FDA** follows a similar course and sets a safety-based threshold with at least a "100 X" safety factor.

VII **A.** Specificat'ns **(P.5.1)** **B.** Analytical Procedures **(P.5.2)**	1176-1231 1250-1253	It would be useful for FDA to allow EP and JP analytical procedures to be referenced rather that needing to provide a copy of the method. This reviewer cannot agree because, as discussed earlier, this matter is not in their control, the **FDC Act** and the **FDA** regulations define what can be referenced. Previously, this reviewer commented to the "SCORECARD" table row containing "358-359" in the column labeled "Guidance Line" as follows: "This reviewer cannot nor can the FDA, bound by US statute, accept the preceding request for clarification."	As stated earlier, the issue of change control management needs to be addressed for EP and JP methods that may be referenced in an NDA. The commenters' remark is not only off the mark but also, *provided the method provided is not **tied or linked** to the EP, JP or any other recognized source*, there is NO "change control issue" in the application. If the filed method is "XYZ-0n3z," then, except for reporting any changes in the method in an annual report, there is no need to file a supplement BECAUSE the method, though derived from some FDA-recognized source initially, has been validated and, *provided it continues to meet its suitability criteria*, is valid. Moreover, the reality is that, in most cases, the written procedures that the labs have and follow are, for good reason, significantly modified (and more detailed) from the written procedure in the **FDA**-recognized source. While these and other commenters have focused on the burden that "in house" test procedures impose, they have overlooked both: **a)** The reality that most labs' analytical procedures are <u>not</u> really the same as the reference procedures (thus, the commenters are proverbially beating a dead horse), and, **b)** If validated and valid, there is no need to file any supplement, all changes can simply be reported in the firm's "annual review" and do <u>not</u> need to be updated each time the **FDA**-recognized source document's analytical procedure is changed, unless the change is to correct a non-validity found in the method (thus, practically, the commenters are, again proverbially, cutting off their own nose to spite their face). For completeness, this reviewer's previous "justification" remarks were" "Given the reality that, by statute, the ONLY official compendia are the USP, NF and the Homeopathic Pharmacopeia of the United States, no other compendium can be recognized as official. Therefore, **a)** the Agency correctly <u>requests</u> such to be listed as "in-house" specifications and tests; and **b)** the commenters have correctly observed, *if such "in-house" specification or method is **<u>tied</u>** to the **JP, JP-E, EP (PhEur), BP** or any other **FDA**-recognized source*, a change in the referenced compendium would trigger the need of the NDA or ANDA holder to file a CBE or, in rare cases, could require a prior approval supplement. However, if the applicant's specification or method is developed from such a source, *but not <u>tied</u> thereto*, there would be no such need. The preceding is true of methods from any other such FDA-recognized source."

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.A (P.5.1)	1194	Insert "more" before "likely". This reviewer agrees.	Grammar
VII.A (P.5.1)	1201	Delete the word "all" This reviewer does not agree, because the change does not clarify the request it changes it. Thus, this reviewer recommends that the text be retained "as is," *unless the drafters, upon reviewing these comments, decide that there is no need to ensure that "all" are provided,* "If sufficient data (e.g., data from multiple batches, all proposed manufacturing sites and processes) are available, a PQIT proposal can be included in the original application.	Clarity For the rationale for a deletion to be "clarity," the change must make clear what the persons who drafted the text have said. The proposed deletion does not do what is required. Moreover, the deletion proposed changes the meaning of the drafters' text. Further, this reviewer resents those who attempt to disguise their actions by deliberately misidentifying the commenters' real reason for the change proposed.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.A (P.5.1)	1214, 1219-1221	Revise to read as follows: "...the PQIT will be performed on each subsequent batch until sufficient data is generated to support the PQIT." This reviewer disagrees, but does recommend modifying the text to address this reviewer's concerns and those of other formal commenters: "The commitment should state that: • the PQIT will be performed according to the protocol approved in the application • failure to meet the acceptance criteria for the PQIT will be handled (e.g., investigation, batch rejection decision) in the same manner as a failure of a test included in the drug product specification and, after the possible causes for the PQIT failure have been identified, appropriate corrective action has been initiated and the *quality control unit* permits production to resume, the PQIT will be performed on each subsequent batch until the ~~failure is~~ all data indicate that the corrective actions taken have truly identified and resolved the root cause or causes of the failure. • any investigation will assess the effect on all batches ~~produced, in particular, the batches~~ between the last batch tested with a passing test result and the **last** batch ~~that failed~~ **tested** • if the result of the investigation confirms a batch failure or is inconclusive, a changes-being-effected supplement will be submitted to include the test in the drug product specification	The commitments imply a large GMP impact. **Re: Rationale:** Because PQIT is beyond (*in addition to*) the *minimums* required for **CGMP** compliance, a firm wishing to implement a PQIT must make such a commitment or the **FDA** should not use said PQIT in judging whether or not to recommend application approval. Moreover, any truly **CGMP** compliant manufacturer wishing to use the PQIT approach should have no objection to committing to do what they propose to do. Any firm who proposes to do anything in an application and who will not commit in writing to meeting any one of the controls they have elected to propose should find have their application summarily rejected. **Re: Comment:** First, the support for the PQIT should have been and must be established before the PQIT was proposed. Second, if the PQIT finds a batch failure, that failure must be treated as any other failure and investigated. Pending the outcome of that investigation, either production must be suspended or the PQIT must become part of the quality controls on each batch. If the results of the investigation find that the root cause of the failure was process instruction ambiguity, operator or lab error and the testing of the batch-representative reserves between the last batch that passed PQIT and the problem batch are batches that meet the PQIT, the PQIT may revert to its periodic interval. In all other cases, the PQIT should become a part of the routine quality testing protocols and a changes-being-effected (CBE) supplement should be filed. **Re: Additional Change** If the PQIT data passed at batch "n" minus 33 ("n-33"), where "n" is the problem batch, then the additional batches that need to be checked are the batches from "n-32" to "n-1." If, *in the interim*, production is allowed by the QCU to resume or continue, the PQIT and other data for batches "n+1" and beyond will speak to the validity/non-validity of the process and should be explicitly included in the investigation. Also, the change addresses investigating batches started but not yet "produced."

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.B (P.5.2)	1254-1257	We propose that microbiology, sterility, bacterial endotoxin tests be exceptions to the requirement to specify which pharmacopeial method, from the options available for these tests, is being used. This reviewer cannot agree for the reasons stated.	Since it is necessary to validate these methods, and since they may be carried out at contract laboratories we recommend for logistical reasons, the filing should specify the "parent" monograph only. The CGMP regulations (**21 CFR 211.160(b)**) require the drug product manufacturer to establish **"scientifically sound and appropriate specifications, standards, sampling plans, and test procedures."** That a manufacturer chooses to adopt a given means of compliance that generates logistical complexity or logistical simplicity is in the control of that firm. Because these laboratories are supposed to be "available" (**21 CFR 211.22(b)**) to firm's quality control unit (QCU), the information about which exact procedure or procedures each such lab, contract or otherwise, uses for all tests must also be available to that same QCU. Since the information is available and in the control of the drug product manufacturer (through the contracts they establish with such labs or, for in-house labs, directly), that information should be provided – perhaps this will help the applicants to see the value of simplifying their supply chain with respect to contract labs as other industries have.
VII.C (P.5.3)	1276-1277	We recommend that the FDA clarify the meaning of the statement; "This information should be provided for all analytical procedures listed in the specifications." Though the meaning of this sentence is clear to the reviewer, this reviewer would propose that the sentence be revised to read: "This **analytical validation** information, **including all experimental data establishing the suitability of the procedures under their actual conditions of use**, should be provided for all analytical procedures listed in the specification (P.5.1).	The level of validation required to demonstrate that analytical procedures are suitable for their intended use varies for each procedure type. In principle, this reviewer is inclined to agree with this statement except that it should have simply stated "... for each procedure" for this reviewer to agree without reservation. Certain procedures 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 products or other selected component(s) in the drug product do not require any information. As a trained Analytical chemist, this reviewer knows that this statement is false. All analytical procedures require the developer thereof to: **a)** prove the procedures' validity, **b)** establish the validity of the operational envelope set for the procedures, and **c)**, when the procedures are used for decision making (control). prove that the specifications established for the procedures are *scientifically sound* and *appropriate*.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.C (P.5.3) (Cont.)	1276-1277 (Continued)		Rationale / Justification (continued) For example, we would not expect to provide validation information for the appearance test in a specification. Though this reviewer would hope that the commenters' firms do validate their "appearance" examinations which broadly are test procedures s under **21 CFR 211.160(a)** and **21 CFR 211.160(b)**, they are technically not analytical test procedures because the samples are, in general, not analyzed – their appearance is simply examined. [**Note**: However, if the appearance specification includes an analytical test quantitativem easurement of the "whiteness" of a "white" tablet against a predefined minimum "whiteness" reference standard, then this test is an analytical test and its validation information should be provided, along with the detailed test procedure, "whiteness" reference standard or standards used, and, if used, the routine "whiteness" check standard.] Therefore, the submission of the validation of such non-analytical tests (examinations) is not being requested, and the commenters' example does not address the issue stated. However, though classifiers like NIR systems may not report quantitative values, they are analytical tests because they make quantitative measurements and then analyze the measurements made to classify the material examined as "acceptable," "unacceptable," or "indeterminate." We might provide verification information for a compendial method. Since "verification of the suitability of a method under actual conditions of use" is an instance of validation, it would seem that the commenters are agreeing to provide validation information for compendial methods. The preceding would satisfy the request provided they also provided the scientifically sound and appropriate (more complete) validation data for all other analytical test methods.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.D. (P.5.4)	1288-1291	While Batch analysis data from all requested lots mat be provided, we understand that all of the batches may be used for the establishment of specifications. Obviously data from batches, needed for other purposes, that do not, *in any manner*, directly or indirectly bear on the establishment of specifications would not be used for this purpose.	The commenters provided no rationale. All specifications should be based on only the data that directly, *or indirectly,* bear on the specifications. However, data that may not directly bear on a given specification (e.g., the uniformity of the active in the final blend on the weight of the tablets) may be critical to establishing a *scientifically sound* and *appropriate* batch specification, for example, the permitted weight range for tablets. This is the case because tablet weight does influence content value in the sense that a doubling of the tablets' weights should approximate double the content of the active in the tablets. Thus, were a final blend to be and remain perfectly uniform, tablet weight and tablet active content correlated, a firm could justify just using the tablet weights in lieu of measuring the active content of a representative set of tablets. Since, in reality, the preceding is only the case for "true" solutions, the manufacturer is required to both measure and control tablet weight and measure tablet active content, active availability, and, where the **USP** or the **FDA** directs, impurities, related compounds, degradants and other moieties,
VII.D. (P.5.4)	1292	A COA does not need to be provided here if collated batch analyses data are included. This reviewer does not agree, but, to improve the specificity of what is being requested recommends that the draft text in **Lines 1288 – 1292** be revised to: "Batch analysis data should be provided for all batches, **from all phases of development, that were** used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies. Batch analysis data should also be provided for any other batches that are being used to establish or justify specifications and/or evaluate consistency in manufacturing. The batch analysis reports (e.g., COAs) and collated batch analyses data should include a description of the batches."	The commenters provided no rationale. The phase "from all phases of development" is suggested to ensure that data bearing on the validity of the test methods used is clearly requested.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.D. (P.5.4)	1301	Container closure should not be included in the metadata for batch analysis. It is not relevant. This reviewer disagrees.	The commenters provided no rationale. The container closure information is relevant because it permits an analysis of the data to include the question of whether or not the differences observed among some test data sets are related to the nature of the container closure system used to hold the samples prior to testing. In this reviewer's experience there have been several instances where test set differences were related to the specific container closure system used.
VII.D. (P.5.4)	1304-1305	Excipient batch numbers should not be mandatory Ironically, this reviewer both agrees with the commenters and disagrees with them. The reviewer would suggest the proper terminology is "batch identifiers" (both here and in the following lines) because not all such are numbers. Based on the preceding, this reviewer recommends that **Lines 1297 – 1305** be changed to: "• Batch identity (i.e., batch ~~number~~ **identifier**), strength, and size • Date of manufacture • Site of manufacture • Manufacturing process, where applicable • Container closure system • Use of batch (e.g., bioavailablility, stability) • Batch ~~number~~ **identifier** of the drug substance used in the drug product • Batch ~~number~~ **identifier** of novel excipients or any excipients that are critical to product performance (e.g., excipients used to form liposomes)"	At the discretion of the sponsor, novel excipient batch numbers could be provided. This reviewer knows that just as it is important to know the container closure system, it is equally important to capture the lot of excipient used. This is the case because each specific lot may affect the batch uniformity or drug product performance with respect to the uniformity of the active and/or its release or release rate from the dosage unit even in cases where the ingredient is not expected to affect either. Moreover, the effect in some cases may be important and may, in turn, require a change in the allowable specification ranges for one or more measured parameters.
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. This reviewer notes that the commenters addressed this very point earlier (**see** commenters' row having an "**Guidance Line**" column identifier starting with "1092-1094,") and, with reservations, agrees.	The commenters provided no rationale.

Section	Guidance Line	Comment / Observation	Rationale / Justification
VII.D. (P.5.4)	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. This reviewer disagrees. →→ For example, batch analysis is not the appropriate place to report the additional testing performed during validation. This reviewer disagrees. →→ We suggest that is inappropriate to require results from all tests that are not part of the proposed specification. This reviewer disagrees. →→ --- Perhaps the requirement should be limited to data in support of named tests, considered for inclusion but omitted on the basis of data, e.g., chiral testing. This reviewer disagrees. →→ --- In addition, not all batches in a batch analysis are considered relevant for certain tests. This reviewer disagrees. →→	To facilitate paperwork reduction, only data relating to test referenced in application in the application should be provided. Since all tests should have been reported, this reviewer does not know what is the point of the commenters' statement. --- Contrary to the commenter's remark, "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.," the results, *not the data* [which is not being requested here], requested: **a)** Are relevant; **b)** Bear directly on **i)** The validity of the testing performed and **ii)** Agency's stated reason for the request "**evaluation of the product quality, safety and performance,**" and **c)** Should be provided. --- This reviewer would again direct the commenters to the preceding remarks made by this reviewer. In addition, this reviewer would remind the commenters that the Agency is entitled to inspect all of the reports and results for the batches in question. --- While the commenters' statement is true, all batches are relevant to some test or tests.
VII.E.2 (P.5.5)	1368	"Active Ingredient" should read "Drug Substance" to provide consistent terminology throughout this guidance document. This reviewer cannot agree; this change is not warranted. However, the text should be corrected as follows: "~~Active ingredient related~~ Active-ingredient-related impurities not covered in S.3.2 can include, for example, degradation products of the active ingredient arising during drug product manufacture or reaction products of the active ingredient with an excipient and/or immediate container closure system."	Clarity The term "drug substance," as defined in the in the Glossary, is a derivative term because it is defined in terms of the term "active ingredient." Moreover, the terms "active ingredient" and "drug substance" are both used throughout this guidance. Based on its definition in **21 CFR 210.3(b)(7),** the use of the term "active ingredient" is proper in the text cited provided the first usage is changed to reflect proper grammar.

Section	Guidance Line	Comment / Observation	Rationale / Justification
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. This reviewer agrees thats ignificant is not defined here, but knows that referencing the guidance ICH Q3B is not the appropriate approach. This reviewer therefore suggest that draft guidance **Lines 1371 – 1372** be changed to: "**Attempts should be made to identify all degradation products found at ~~significant levels~~ in the drug product** at levels that, based on both appropriate acute toxicity studies and short-term chronic toxicity studies, are found to be a potential safety or health hazard.	Clarification, harmonization Since the primary reason for the identification of any unknown substance in a drug product must be its potential effect on patient health and safety. Thus, instead of the nebulous "at significant levels," the text needs to reflect the preceding reality. The appropriate safety control levels (Threshold Limit Values) for many known chemicals are less than 100 ppm (<0.01 %) and more than a few are less than 100 ppb (<0.0001%). In contrast, the ICH guidance sets a general level of 0.1 % – a level that is not always safe. [**Note:** This is the approach the **EPA** "adopted" for impurities in biocides in the 1970's, perhaps, in 2003, the **FDA** will, as it should, do likewise.]
VII.E.	1386-1391	Revise as follows: "~~An applicant is aware of the~~ If solvents are used in the manufacture of the drug product, ~~a nd in most cases those being introduced from other sources (e.g., drug substances, excipients). Because these are known,~~ the identity and presence of residual solvents in the finished drug product should be established and controlled. Solvents introduced from drug substances and excipients should be controlled at the drug substance and excipient level, not at the drug product level. ~~Can uaually be confirmed bysuing routine analytical techniques. In some cases, structural characterization of an unknown impurity can determine that the impurity is a residual solvent.~~" This reviewer disagrees with the proposed changes and would recommend leaving the text as it is. This is the case because of the cost savings manufacturers will save by using well-characterized excipients from reputable sources as opposed to excipients that are less well characterized or from sources that may be in some sense "counterfeit"	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. All that the text provided here does is simply remind the applicant of what is expected of the applicant. The alternative offered by the commenters is not as informative of what the applicants should be aware of as the draft test does. Moreover, the text in context does NOT address the level of control, it addresses the issue of listing – regardless of where and how they are controlled, the applicant is simply requested to identify and list those that are present in the drug product. The real impact of an applicant's doing what is suggested would be a good thing – to eliminate those vendors that cannot supply the requisite data from the applicant's approved vendors list. What manufacturer wants to be saddled with identifying the impurities in the excipient ingredients?

Section	Guidance Line	Comment / Observation	Rationale / Justification
IX. (p.7)	1531	The guidance should mention the container closure system for the proposed marketed drug product. While this reviewer understands the import of this somewhat cryptic comment, this reviewer would propose also including the container closure systems used for retain samples of the drug products or components, any stability study, and any clinical study involving humans. Based on the preceding, this reviewer would propose; "A description of the container closure system **or systems** for the drug product **(including the systems for the proposed marketed drug product, the drug product retain samples, and any system used in any drug-product stability protocol)** should be provided, including the identity of materials of construction of each primary packaging component and its specification. **An abbreviated description of the container closure system used for** the component retain samples should also be provided. The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. Information about the suitability of a container closure system should be provided in P 2.4.	The commenters provided no rationale. Since the choice of container closure system is important for any packaged system used for a regulated purpose, those systems should be clearly spelled out.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IX. (P.7)	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 that 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." This reviewer agrees that a definition is needed and that the commenters' definition is a good start but would suggest that the following alternative be considered: "Functional secondary packaging: Packaging that ensures that the product meets the necessary quality criteria by offering **added** protection **from environmental degradants (for example, light, water, oxygen, and carbon dioxide)** or by enabling appropriate and accurate metering and dosing of the product."	The commenters provided no separate rationale to support their definition. The need for a simple useful definition of the term "functional secondary packaging" is evident and it lack impedes a common understanding of precisely what the definition encompasses. The commenters' proposed definition is an excellent start. However, this reviewer proposes what it does in the area of "protection against degradation" is better expressed in terms of what it adds. The preceding is the case because it, in fact, does not protect from degradation, it adds protection from those environmental factors that would increase degradation.

Section	Guidance Line	Comment / Observation	Rationale / Justification
		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 tabulations of stability data in stability tables. This reviewer does not agree that the "results of stability studies" are the same as "stability study reports." "Stability study reports" are the appropriate summaries of each stability study record (**21 CFR 211.194(e)**) and, at a minimum, should include items (1), (2), (6) and the names from items (7) and (8) of the requirements for a stability record (**21 CFR 211.194(a)**) Most important of these, beyond the results themselves, is the statement of how the results compare to the established standards (in this case, the baseline batch-representative data for the batch being tested) of identity, strength, quality, and purity for the finished packaged drug product tested including, if required the packaging integrity tests (for example, the observed container closure opening torque for drug products sensitive to moisture packaged in bottles and, if used, the residual moisture absorbing capacity of the desiccant pack or packs in the container).	Clarification The results are but a small part of the CGMP requirements for " Complete records shall be maintained of all stability testing performed in accordance with Sec. 211.166 (**21 CFR 211.194(e)**) Further, 21 CFR 211.194(a) "Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows: (1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing. (2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is ..., a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use. (3) A statement of the weight or measure of sample used for each test, where appropriate. (4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested. (5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors. (6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested. (7) The initials or signature of the person who performs each test and the date(s) the tests were performed. (8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards." Based on the preceding stability study reports need to summarize the important information, results and findings of the testing. Since the purpose of stability testing is to asses stability, a stability report must do that for every test station and interval. Based on the preceding, the commenters should see that much more than a reporting of the results is needed and should better understand the CGMP basisf rom which that request was generated. Finally, being requested to submit stability reports is far better than being requested to submit the stability records.

Section	Guidance Line	Comment / Observation	Rationale / Justification
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 reviewer disagrees and believes the draft guidance text should remain: "**A summary of any changes in the analytical procedures should be provided if the analytical procedure was changed over the course of generating the stability data. ...**"	This would eliminate the need to report trivial changes. The introduction of the word "significant" introduces a subjective decision element as to what changes are significant (and which are not) when, in fact, any change in the validated analytical procedures should be reported because, unless it had some effect, that change probably would have not have been made. Moreover, the inexplicable deletion of the phrase "**in the analytical procedures**" and the substitution of the less precise, "that would impact the results" again substitutes the definite for the less definite. Finally, in this reviewer's experience as an Analytical chemist, this reviewer has never seen a change in a stability method that was trivial because, rightly, prudent firms initially generate and validate their stability methods with the aim of having a method so well defined that their projected change dates are at least twice that of the dating period to minimize the risk of problems in interpreting the stability data caused by a changed-induced discontinuity in the results obtained.
X.C. (P.8.3)	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 method. This reviewer disagrees with the commenter.	Clarity First the commenters' statement states a preference that they may choose to follow. However, nothing in the guidance is so prescriptive as to request that this is the only way to structure the reporting of stability information requested here. Moreover, this reviewer does <u>not</u> agree that P.5.1 and P.5.2 can, or should, be viewed as the complete statement of regulatory methods. Finally, the structuring of the CTD was carefully thought out and, where and as needed, the option to reference information in other methods was provided.
X.C. (P.8.3)	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" This reviewer concurs that the addition of the initial clause "Based on the dosing directions included in the product labeling," would clarify the text but that the other change "**Information regarding the compatibility of the drug product**" with "compatibility data" does <u>not</u>.	Clarity The clarity added by the first change is offset by the reduced clarity of the second. This reviewer would propose to accept the first and change the text to, "Based on dosing directions included in the product labeling, **information regarding the compatibility of the drug product with any diluents (i.e., constitution, dilution of concentrates, admixing), dosage devices, or coadministered drug products should be provided in P.2.6.**" Information should be data plus interpretation thereof

Section	Guidance Line	Comment / Observation	Rationale / Justification
X.C. (P.8.3)	1607-1609	Delete sentence on providing stability data to support holding of materials. This reviewer disagrees and would propose the following text restructuring and modification (**Lines 1603 – 1607**) to address the commenters' concern: "Data, other than those from formal stability studies, that support the analytical procedures, the proposed shelf life, and label storage statements can be provided. Such data can include, for example, stability data on ~~small-scale~~ **small-scale** batches of drug product, investigational formulations not proposed for marketing, related formulations, or product presented in container closure systems other than those proposed for marketing. **In a separate identified subsection, the stability** ~~Stability~~ data to support holding in-process materials for longer than 30 days should also bep rovided ~~in this section~~ **here**. Information on the type of container closure system in which the in-process material is held should be included with the stability data **in all cases**. The analytical procedures should be identified, and when analytical procedures are different from those described elsewhere in the application, information should be provided on the analytical procedures to the extent warranted to support the use of the data."	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. [This text relocated to the "Rationale" column because that is what it is.] The commenters admit that this information is a) necessary; b) stability data, and c) is being requested in the section dealing with stability information. The commenters propose no text to effect their proposal to move it. The issue of confusion can be addressed by requesting that it be placed in a separate subsection.
X.C. (P.8.3)	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. This reviewer does <u>not</u> agree; the text should remain as it is (**Lines 1617 – 1622**), "Any results from drug product stress testing and thermal cycling studies should be provided in this section of the application. The design of the stress studies should be discussed briefly. The information should be used, as appropriate, to support the validation of analytical procedures (P.5.3), the impurities acceptance criteria and/or characterization of expected impurities (P.5.1, P.5.5), justification of the drug product specification (P.5.6), and stability summary and conclusions (P.8.1)."	If the results of stress studies do not impact these items they need not be included; the first sentence of this paragraph suggested otherwise. [This text relocated to the "Rationale" column because that is what it is.] The reality that, by their very nature, the results from stress and thermal cycling serve to support, or cast doubt on the validation of the methods used to test the samples from those studies. Thus, all such studies should be reported – <u>not</u> only those that support, but also those that cast doubt on, the validation of the items specified. The commenters' proposal would permit the applicant to exclude studies where the results obtained do <u>not</u> support item validity.

Section	Guidance Line	Comment / Observation	Rationale / Justification
XI.C Appendices (A.3)	1762-1763	Change "IV.B.2" to "IV.A.2". This reviewer concurs.	Incorrect section is referenced.
XII.A.1 (R.1.P)	1793-1795;	Delete "Phase III clinical," This reviewer agrees. If the Agency feels the EPRs from the Phase III clinical studies should be submitted, this reviewer recommends the following text: "**Executed Production Records (EPRs) for representative batches used in Phase III clinical, bioavailability, bioequivalence, or primary stability studies and supporting production information must be provided (21 CFR 314.50(d)(1)(ii)(*b*)).** EPRs for the Phase III clinical batches should also be submitted in support of the validity of the results obtained and the test procedures used therein.	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 the 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 the information is more appropriately summarized within the application, not in providing additional volumes of batch records. The commenters provided no rationale. Either the commenters seem to have not read all of, or this reviewer seems to have misread Section XII.A.*1.*, **Lines 1799** through **1804** (**bolding** emphasis added), "**For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted. In cases where clinical batches used in Phase III trials were less than pilot scale, submission of the EPR for the largest scale clinical batch is also recommended. Discussion of which EPRs should be included in the NDA can be a topic at pre-NDA meetings. For ANDA submissions, EPRs should be submitted for the batches produced in support of the application.**" Based on all of the text in this paragraph, the commenters' suggestion is verbiage that is: **a)** unnecessary for the NDA case and **b)** counter to the Agency's request in the second case. Had the Agency felt that there was a need to counsel ANDA submitters on the nature of the batches to submit, they would have said so. Had the Agency felt that only one batch per strength was appropriate in either case they would have said so. Based on this reviewer's personal experience, the Agency is aware that there have been times that firms submitting ANDA information from only one batch per strength concealed, by choosing the "best" batch, serious process and drug product problems and obtained approval.
	1799-1801	Add the following: "In cases of multiple strengths, one batch per strength is typically sufficient for submission." This reviewer disagrees.	

Section	Guidance Line	Comment / Observation	Rationale / Justification
Xii.B (R.2.P Compar-ability 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..." This reviewer disagrees; but recognizing that statistics cannot prove or disprove any hypothesis, "null" or otherwise, would recommend the following changes to address that issue (**Lines 1826 – 1833**): "A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the apparent lack of adverse effect for specified types of postapproval manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety and effectiveness of the drug product. The proposed sampling plans for outcomes based on the testing of the drug product in comparability protocols should be based on the sampling and testing of sufficient representative samples from the batches being compared to ensure, *at a confidence level of 95 % or higher*, that the batches in the comparison are predicted to conform to the drug-product-release variable factor ranges established in a drug–product specification that fully complies with the statistical quality control (SQC) requirements set forth in **21 CFR 211.165(d)** as well as the **CGMP** requirements for drug-product release set forth in **Sec. 211.160**, **211.165**, and **211.167**. Comparability protocols are optional. If a comparability protocol is proposed, it should be included in this section (R.2.P). Approval of a comparability protocol can justify a reduced reporting category for the particular postapproval change described in the protocol."	From a statistical point of view, one cannot demonstrate (prove) a lack of effect (null hypothesis). Though the commenters' remark is technically true, its use is misleading and inappropriate. Factually, statistics cannot be used to prove any hypothesis. Statistics only establishes (proves), at some population and confidence levels, the probability that a given hypothesis may be true. A comparability protocol can only give evidence that an effect is within an acceptable range. Factually, a properly designed comparability protocol can, by using population statistics, predict, *at some confidence level*, the degree to which batches produced with a change are the "same" *with respect to all* ***CGMP****-regulated parameters* as the batches produced prior to the changes provided the comparison has and uses valid results data for all **CGMP***-regulated parameters* from sufficient *batch-representative* samples from the sets of batches being compared. Thus, the commenters' statement is not factually correct. Moreover, if, as has often been done on the past, the comparison is from too few or non-representative samples, all that a protocol can do is compare the results obtained in each case to the **USP**'s post-approval in-process specifications and then state whether or not the samples tested happen to meet **USP** expectations. Further, it is not scientifically sound to directly compare different sets of results from samples that are not provably *population representative* at some significant (a "γ" of 0.9 or higher) confidence level whether it be in a comparability protocol or elsewhere. A comparability protocol is an equivalence test (not a hypothesis test), but cannot demonstrate lack of effect. Factually, a comparability protocol is not a test it is, by definition, a document. Moreover, the design of the experiments set forth in a protocol determine what the outcomes of the testing specified can or cannot demonstrate; not the rhetoric of the commenters nor, for that mater, that of this reviewer.

Section	Guidance Line	Comment / Observation	Rationale / Justification
Attach-ment 1	1921	The Microbial Limits for specific dosage forms will be specified in USP <1111> Microbiological Attributes of Non-Sterile Pharmaceutical Products. This reviewer does not agree and would propose keeping the guidance text as it is in the draft, "**Acceptance criteria should be provided for total aerobic microbial count, for total combined molds and yeasts count, and for absence of designated microbial species (e.g., Staphlococcus aureus, Escherichia coli, Salmonella species, Pseudomonas aeruginosa).**"	The absence of specified microorganism requirements would depend on the dosage form First, the **USP General Chapter <1111>** is, as are all such having <identifiers> of "1000" or higher, only a guidance chapter and not a **USP** requirement chapter. Second, while the requirements do, to some degree, depend upon the dosage form, the applicant should: **a)** establish and justify two limits, release and lifetime, and **b)** ensure that their drug products are free of designated organisms for which some or all strains are known safety risks to those that will consume the proposed drug product. Thus, at best, **USP <1111>** can only be used as part of the justification for the *lifetime* limits. Other measures should be taken to justify the *release limits* specified in the application.
Attach-ment 1	2010	Reference to USP <61> acceptance criteria for total aerobic microbial count is not appropriate for transdermal patches. This reviewer agrees with this statement but doesn't see its appropriateness here and recommends that the draft text be maintained as it is (**Lines** 2008 — 2010), "• **Microbial Limits** **See information provided under semisolids.**"	The microbial limits for transdermal patches are based on the surface area of the patch, not its weight. Because this document is guidance and its test here is a reference to other guidance, the applicant is not bound to follow it at all – much less by rote. Moreover, this reviewer recommends that the commenters take this issue up with the **USP** so that **General Chapter <61>** is appropriately modified or the **USP** adds a separate General Chapter for patches.
Attach-ment 1	2061	It is recommended that the document cite USP <51> Antimicrobial Effectiveness Tests for the method for preservative effectiveness.	The commenters provided no rationale.

Section	Guidance Line	Comment / Observation	Rationale / Justification
Glossary	2117-2256	Consider adding the following list of terms: Critical Process Control Critical Step Critical Tests This reviewer disagrees; the guidance only need define the word "critical" as this reviewer proposes.	The commenters provided no rationale. **See Reviewers' remarks to Commenters' General Observation 1.** **Critical:** Of or pertaining to any entity that is required to be controlled in a manner that complies with, or governed by any requirement specified in, the drug **CGMP** as set forth in **21 CFR Parts 210** through **226**. Examples include, but are not limited to, critical control, critical factor range, critical phase, critical process control, critical process phase, critical specification, critical statistical quality control, critical step, and critical test, "
		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 This reviewer disagrees. →→	**See Reviewers remarks in the "SCORECARD" table row identified in the column labeled "Guidance Line" as "437."**
		Non-compendial Excipient This commenter agrees and suggests using the form "noncompendial" instead of the more grammatically proper "non-compendial" to save paper.	**Noncompendial Excipient:** An excipient that is not defined in a monograph or chapter in any official compendium.
		Novel Excipient – add suggested definition This reviewer agrees	**Novel Excipient:** An excipient that is used in the United States for the first time in a human drug product or delivered by a new route of administration. Any excipient that is not a "novel excipient" is "non-novel excipient."
		Sunset Testing This reviewer agrees.	
		This reviewer also proposes to add the following: **Actual specification**: The specification that the applicant actually uses for the drug substance or component for a given analytical test or examination. For example, the compendial specification for the pH of an ingredient might be "4.0 to 7.2," but the applicant's actual pH specification for that ingredient is "4.3 to 6.9."	Based on the commenters' remarks in the "SCORECARD" table row identified in the "Guidance Line" column as "759-761," a definition of this term is needed in this guidance document This reviewer therefore has proposed a definition with example for inclusion in the CMC guidance

Section	Guidance Line	Comment / Observation	Rationale / Justification
Glossary (Cont.)	2117-2256 (Continued)	Consider adding the following list of terms: (continued) Based on requests made by the commenters and a definition they proposed and this reviewer revised, the following definitions are offered: **Compendial Monograph:** Any currently official monograph in an official compendium. The same as: "**Official Compendial Monograph**" [**Note:** No pharmacopeia, or portion thereof, other than those that are recognized by the FDC Act as an "official compendium" is, for the purposes of any CGMP regulation or guidance, a "compendium or", in the case of a portion thereof, "compendial." Thus,a ll proper uses of the term "compendium" or "compendial" pertain to an "official compendium" because these are defined by statute.] **Criterion:** Any established rule (specification) by which an accept/reject decision can be made. The plural form of "criterion" is "criteria." **Functional Secondary Packaging:** Packaging that ensures that the product meets the necessary quality criteria by offering added protection from environmental degradants (for example, light, water, oxygen, and carbon dioxide) or by enabling appropriate and accurate metering and dosing of the product." Reprocessing Reworking	The definition and its companion note proposed here are offered to address issues and comments made by these commenters. The definition proposed here is offered in response to the commenters' request for it. The definition proposed here is this reviewer's revision to the definition proposed by the commenters who, noting its absence inth e referenced guidance, proposed adding it to the Glossary This reviewer was surprised that the commenters did not mention adding these because their comments in the "**SCORECARD**" table row identified in the column labeled "**Guidance Line**" as "887-912" indicated that definitions for "reprocessing" and "reworking" should be added in the Glossary.

A Review of Formal Comments To Public Docket 02D-0526

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

GPhA's Submission Dated July 7, 2003 To Docket 02D-0526: "C-15"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow.]

With respect to the comments submitted by the GPhA (Generic Pharmaceutical Association), please consider the following.

As the commenters state, "GPhA represents 98% of generic drug manufacturers whose drugs are dispensed for almost half of all prescriptions tilled in the United States, but representing less than 10% of all drug expenditures. GPhA is the united voice of the generic drug industry and is committed to patient health and safety, and strongly supports any measures that will improve our health care system."

"GPhA has concerns related to the proposed recommendations that comprehensive Pharmaceutical Development reports are to be submitted with each application. The Draft Guidance does not appear to provide for flexibility in regard to content of the reports or when such reports may not be necessary. It is believed that there is a substantial number of ANDAs for which Pharmaceutical Development reports are either not necessary, or could be provided in an abbreviated format."

Contrary to what the GPhA *believes*, the Pharmaceutical Development reports (or an equivalent presentation of the scientific rationale and data that support thea pplicant's submission) for ANDAs are <u>not</u> only necessary in all cases but must, in some areas, be more detailed than those of the NDA application.

Except for the growing trend for the NDA holder to file an ANDA which, <u>provided</u> the NDA is CGMP-compliant, need only reference the approved NDA, this is the case because the ANDA applicant must prove that their formulation and drug product are the same as those of the innovator without having the benefit of being able to review the innovator's submission documents.

Thus, the ANDA applicant must reverse engineer the innovator's drug product and, when they have accomplished that, provide all of the proof that establishes that their drug product is essentially the same as the innovator's drug product even though the ANDA applicant uses a different source for the active pharmaceutical ingredient or ingredients and other components that differ, to varying degrees, in source, nature or amount from the innovator's NDA components.

In this reviewer's personal experience, this reviewer has seen cases where the ANDA applicant failed to develop a drug product (an extended-release drug product) that was the same as the innovators simply because they failed to test an adequate number of the innovator's lots to discover what were the performance variabilities and apparent targets for the innovator's drug product.

What they did was test a few samples from three (3) different lots and a couple of trial formulations (made from a single lot of each component) and then select the innovator's lot whose test results on a few tablets happened to match the test results on a few tablets from one of the two trial lots.

The result was that the firm developed a formulation to match the data from the few samples tested from one innovator lot and submitted an ANDA that basically makes a product like that one innovator lot (which happens to be on one edge of the innovator's performance envelope with respect to drug release.

Although the firm's ANDA was approved, that firm's drug productd oes not have the same "Drug Release" profile as the innovator's NDA drug product – it has a "Drug Release" profile that matched one (1) batch of the innovator's drug product.

"Reducing the content of theses reports or eliminating inclusion of Pharmaceutical Development reports when such reports are unnecessary will conserve valuable FDA resources while continuing to assure that all critical technical information is available for agency review."

Since the information required in Development Reports is critical technical information, this reviewer disagrees with this statement for the same previously stated reasons.

"Providing flexibility in the final guidance document will work to streamline the review process without sacrificing scientific information that is essential to the review and approval process."

Again, this reviewer is all for anything that will facilitate the review process without compromising its integrity and knows that a well-prepared scientifically sound and detailed Development Report is "essential to the review and approval process."

"An ANDA for a generic version of a brand-name drug product (the reference product) must be pharmaceutically equivalent and bioequivalent to that reference product."

Would that the preceding were the case (see preceding comments).

Mostly agree with what has been stated but "bioequivalent to the reference product" all too often becomes bioequivalentt o some one batch of the reference product – not at all the same thing.

"ANDA applicants must show that the generic drug contains the same active ingredient(s) as the brand-name drug product, is identical in dosage form, strength, and route of administration, has the same conditions of use, and is bioequivalent to the reference product."

Again, the GPhA's comments are close to what is reality but the differences are significant.

The ANDA applicant must show that the active(s) in the active ingredient(s) are the same.

However, they may differ to varying degrees from the active ingredients in the innovator's drug product in, for example, their impurity profiles, trace metals fingerprints, bulk physical properties, morphology, intrinsic form and other properties including the processes used in their manufacture.

"Generic drugs must meet all drug product quality characteristics established by the agency as well as any compendial requirements for identity, strength, quality, and purity. Additionally, all drug products must be manufactured under the same strict good manufacturing practice regulations."

This reviewer concurs with the commenters' first statement.

But notes that the requirement is that all drug products must be manufactured in a manner that ensures both their manufacture and the drug product manufactured conform to the requirement *minimums* established in the CGMP (current good manufacturing practice) regulations and not, as the commenters state, "all drug products must be manufactured under the same strict good manufacturing practice regulations."

This reviewer trusts that the commenters do know the difference between the legally defined "**CGMP**" regulations (**21 CFR Parts 210** through **226**) and the legally undefined strict "GMP" regulations that may apply in jurisdictions outside of that of the ***United States of America***.

For certain dosage forms, ANDA applicants must use the same inactive ingredients in the same concentrations as the reference products."

For those dosage forms that are in the majority, there is no requirement that the inactives be the same much less in the same concentrations as the reference products.

Even when the preceding is the case, there is no requirement that these "inactive ingredients" be from the same supplier or manufactured using the same process.

As more than a few have found out, ingredients from different sources may look the same but, in critical areas, such as formulation stability and active stability, provide different outcomes for some lots from some sources or, in some cases, all lots from a given source.

"For example, 21 CFR 314.94(a)(9) identifies certain regulatory requirements for parenteral, ophthalmic and topical dosage forms that are submitted as ANDAs. For parenteral and ophthalmic drug products, the formulation of the generic product must be essentially the same as the brand product."

Even in these cases, the formulation is only required to be "essentially the same as the brand product" – NOT the same as.

"Thus, the value of product development reports for formulations that are either identical or essentially the same as the brand product that have been carefully reviewed and found to be acceptable by FDA is questionable. In these circumstances, FDA would be re-reviewing duplicative information that provides no additional insight into the quality characteristics of the drug product."

Contrary to the position stated, a proper "Development Report" would facilitate the review in such cases by providing the reviewer the proof that the ANDA applicant has met the requirements.

Lacking such proof, the reviewer's time will be wasted because the requisite proofs have not been submitted.

At best, when there is a proof deficiency, the reviewer will put the review on hold and notify the applicant of a proof deficiency – thus delaying the review process.

"As noted, the Draft Guidance does not appear to contemplate those situations when Pharmaceutical Development reports do not provide any useful scientific information. For example, at line 364, the Draft Guidance states that '**The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbial attributes, and usage instructions are appropriate for the purpose specified in the application.**' This statement indicates that a Pharmaceutical Development report will be required even though many generic products are identical in formulation and container closure system to the brand product."

Please read the prior comments addressing this issue.

Moreover, unless the ANDA applicant is the NDA holder (even when this is the case the following may be true), no generic product can be truly IDENTICAL in formulation and container closure system to the brand product.

Therefore, the statement is, at best, meaningless.

Moreover, because the state of *current good manufacturing practice* ("**CGMP**") is supposedly improving as time passes, the NDA holder may need to submit a Development Report that addresses issues that 15 years earlier were not issues, but may still need to be addressed because of the maturation of the expectations for what constitutes **CGMP** compliance today.

For example, the applicant may need to address TSE issues that were not even recognized as an issue 10 years ago.

"Product attributes for generic versions of brand-name drug products such as dosage form, and in many cases formulation and usage instructions (conditions of use), are predetermined by those of the reference product. The ANDA applicant therefore would not likely need to conduct development studies to determine if these attributes are appropriate since they mimic the innovator product."

However, the applicant is required to conduct development studies to establish that the applicant's "same" dosage-form drug product batches PERFORM the same as the innovator's drug product batches.

Moreover, developmental studies for the formulation used to make the applicant's dosage-form drug-product batches are often involved iterative processes that needs to be provided to the reviewer so that he or she may assess whether or not the studies done have met the stated requirements or merely that a few *non-batch-* or *non-process- representative* dosage units happened to give test results close to the few results for a few units from a single batch of innovator's product used as reference (instead of, what should be the case under **CGMP**, the results form a *statistically significant* number of *representative* sets of samples from the applicant's batches being compared to the results from a *statistically significant* number of *product-representative* samples chosen at random from a composite made from sufficient batches to ensure that the results obtained for the innovator's samples are *drug-product representative* – not, *as usually the case*, from one particular lot chosen because its test results most closely match the applicant's test results from "Dissolution" or "Drug Release" tests).

"Similarly, microbial and container closure system attributes (e.g., tight, light resistant container) may be specified in an official monograph and ANDAs must contain information showing that the selected container closure systems are suitable and appropriate for their intended use."

And the Development Report must show how the applicant (ANDA or NDA) established (proved) that said items from the suppliers specified are truly "suitable and appropriate for their intended use."

From the initial "believe" comments, it would seem that the GPhA is an advocate of a faith-based approach to filings.

Fortunately, **CGMP** (as set forth in the **Food, Drug, and Cosmetic Act (21 U.S.C. Title 9, "FDC Act")** and enunciated in the drug **CGMP** regulations set forth in **21 CFR Parts 210** through **226**) established requirements for a science-based (establish, justify, validate, prove, demonstrate, show) approach.

"Thus, ANDAs already contain substantial information related to the container closure system and whether a particular type of container is identified in the USP monograph. Reviewing the same Pharmaceutical Development information in one or multiple ANDAs that has already been found acceptable by the agency results in a waste of resources that could be better used to review other technical issues within the application or to review additional pending applications."

While the preceding is true in part, the reality is that lacking the proofs that the particular container closure system from the supplier the applicant has chosen is "acceptable," the reviewer has no basis to accept that the systems chosen are "suitable and appropriate for their intended use" – a requirement that even the GPhA accepts as valid.

"Also, beginning at line 383, the draft guidance states that "Key physicochemical characteristics ... should be discussed. However, for ANDAs, characteristics such as water, solubility, particle size (e.g., "micronized"), polymorphic form, etc., may be predetermined by an official monograph, or may be specified in the reference product labeling. Thus, the critical attributes have already been established in many cases. It is expected that the Pharmaceutical Development reports for these examples would have little relevant value."

Since this reviewer knows of no innovator product where:

a) All of the key physiochemical characteristics of the components in an NDA product are specified in the innovator's product labeling,
b) The exact particle size distribution that the innovator uses is specified in the official monograph for the active or actives in the innovator's drug product, or
c) Except for morphology and solvation in a few cases, any of the other key physiochemical attributes such as intrinsic dissolution, flow, affinity, etc),

the last sentence references a hypothetical non-existent case.

Moreover, water and solubility are <u>not</u> key physiochemical characteristics – the nature and state of hydration and intrinsic solubility are physiochemical properties that may be key in the formulation used by the innovator.

However, the ANDA applicant may have different, or different values for, the key physiochemical properties for the components that combine in the

applicant's process to produce drug product units that have the same performance as the innovator's drug product.

Further, in this reviewer's limited experience (15+ years) of experience with ANDA products and the development thereof, this is one area where many companies don't do their homework.

The result has been, more often than not, that a "minor" process change by a component supplier leads to batches that fail their specifications and no one in the firm knows "why."

In several cases, the ANDA holder has had to abandon an approved ANDA.

In one particularly sad case, the product failed in validation after approval – thus wasting all of the firm's developmental effort and all of the Food and Drug Administration's ("FDA's") investment in the review of that application.

In all such cases, not only has the ANDA holder's failures in this area usually cost the firm the product, but it has also effectively wasted the review time invested by the FDA.

"The NDA applicant must conduct compatibility studies to provide information to establish and support anticipated usage. The ANDA applicant must duplicate compatibility studies of the drug product admixed with diluents identified in the reference product labeling to show that the generic drug will be compatible under the same conditions of use as the reference product. Pharmaceutical development activity for the ANDA applicant is designed to duplicate the compatibility and conditions of the reference product. From a development standpoint, the objective of the generic applicant is to demonstrate that the product performs the same as the brand product and not to introduce new or novel information related to the formulation or labeling claims.

The commenters' remarks are simplistic and fail to recognize the differences inherent in the "same" components from different sources that usually have differing physiochemical properties.

Proof of compatibility is required – not speculative commentary on the sameness of materials that are KNOWN, at many levels, to differ slightly."

"Recommendation: The Draft Guidance does not describe the need or relevance of Pharmaceutical Development reports for a substantial portion of the ANDAs submitted to FDA. GPhA requests that FDA reconsider the requirements set forth in the Draft Guidance as they pertain to Pharmaceutical Development reports. It is requested that the final guidance provide for a flexible approach that seeks such reports when justified for the limited subset of products for which knowledge of pharmaceutical development activities may substantially contribute to the assessment of drug product quality. For many products, a simple confirmation that the formulation is essentially the same as the reference listed drug, the container closure is the same as that used by the brand product, or the product and container complies with a compendial monograph, provides assurance that there are no new issues raised in regard to the development of the proposed drug product."

For all of the scientific reasons set forth in the reviewer's preceding comments and because of the clear **CGMP** requirements for documented proof of claims, the GPhA's recommendation should be rejected.

"In summary, a Pharmaceutical Development section should be requested for ANDAs only if it adds reasonable value to the review and approval process. FDA should consider identifying the types of

ANDAs that may warrant submission of a pharmaceutical development report and request the reports only in those instances. As stated, a significant number of ANDAs are the same or essentially the same in formulation, container closure system, physiochemical properties, etc., as the reference listed drug. For these applications, a substantive pharmaceutical development report provides no new or relevant information to support drug product quality concerns nor would these reports represent additional scientific support for the proposed drug product. Rather, the resources required to review duplicative pharmaceutical development reports that do not add value to the scientific body of knowledge would not be justified, especially as the agency works towards a more streamlined and scientifically based review process."

The preceding is summary merely restates the unsubstantiated claims refuted in earlier comments.

Given the GPhA's focus, this reviewer recommends the FDA tighten up the requirements for ANDAs to address the issues that I have raised with the aim of reducing the time wasted by inherently weak ANDAs that fail post approval.

A Review of Formal Comments To Public Docket 02D-0526

Baxter Healthcare's Submission Dated June 25, 2003 To Docket 02D-0526: "C-14"

(Federal Register Notice January 28,2003 (FR, Vol. 68, No. 18, Pages 4219-4220)

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow.]

"General Comments:

1. Baxter appreciates and supports the Agency's recommendations on the CMC information for drug products that should be submitted in original NDAs and ANDAs in CTD format. The draft guidance is applicable to generic products, but does not contain specific information relative to ANDAs. Some examples include: line 149 states that the application should include information in every P subsection, but some sections may not apply to a generic product such as P.2.2.1 Formulation Development; lines 667-673 discuss the compatibility of drug products with diluents and the necessity of performing compatibility studies, but such studies may not apply to a generic product. Specific notations where the guidance does not apply to generic drug products or where requirements for generic drug products may be different would help to clarify the recommendations."

This reviewer suggests that Baxter read this reviewer's review of the documents submitted by PhRMA (C-16) and GPhA (C-15) to understand that such truly are musts for ANDA as well as NDA applications even though the purpose and critical issues may differ between the two types of applications.

"2. In general, this draft guidance document should be consistent with the ICH guidance documents. In some areas, such as the Characterization of Impurities section V.II.E. below, this new guidance attempts to broaden the scope of the ICH guidances."

Provided the **Food and Drug Administration** ("**FDA**") guidance properly addresses ALL of the *current good manufacturing* ("**CGMP**") requirements, then, to the extent possible, the **FDA**-sanctioned ICH guidances should be followed.

However, in areas where the ICH guidances fail to meet all of the requirements of **CGMP** or where the ICH guidances differ from *sound science*, the **FDA** should propose guidance to the Chemistry, Manufacturing, and Controls ("CMC") section of an application that is based on *sound science* and *compliance* with the **CGMP** *minimums* for drugs and drug products without regard to the ICH guidance.

"Specific Comments:

Section IILC. Composition Statement
Please clarify what is meant by 'per unit basis' in lines 327-329?"

"**Table 1: Example Target Composition Statement,**" provides a tablet case.

In that example, the unit is the "tablet" and all amounts are based on the target amount in that a given strength tablet.

"Section TV.B. Drug Product, 2. Overages

Lines 537 - 539 state that use of an overage of drug substance to compensate for degradation during manufacture or shelf-life is not appropriate. The drug GMPs allow for the formulation of a drug product to meet label claims. Please clarify what is meant by degradation vs. manufacturing loss. Manufacturing losses may occur due to filtration or other means besides degradation."

Lines 537 – 539 actually state, "**In general, use of an overage to compensate for degradation during manufacture or a product's shelf life, or to extend the expiration period, is not appropriate.**" (**Bolding added.**)

Thus, an applicant will need to justify any overage added to compensate for such losses.

However, this draft does not, as the commenters' remark suggest, prohibit formulations that have such overages.

Manufacturing losses are any non-degrative losses that the product experiences during normal or routine manufacture.

Degradation losses are losses where a portion of an active is converted into another chemical structure or other chemical structures by reaction with that is initiated by a manufacturing condition such as moisture, heat, light, component interaction, or a trace impurity that reacts with or catalyzes the decomposition of an active.

"Section IV.F. Compatibility
Lines 661 and 662 are very broad, covering many possible device categories. Please clarify that compatibility studies should assess devices and administration sets only if they are specifically indicated in the drug product labeling."

As written, the preceding test and the following sentence, "**The design and extent of the compatibility studies depends upon the type of drug product and its anticipated usage,**" make it clear that the type and nature of the "**for example**" studies mentioned in **Lines 661** though **662** depend upon the drug product's "**anticipated usage.**"

Thus, an applicant need only "assess devices and administration sets" when "**the anticipated usage**" requires such.

"Section V.A. Manufacturer
Please clarify that lines 693-695, sterile processing area (room and filling line), apply to aseptic processing only and not terminally sterilized drug products."

As written, the need to list the "**sterile processing area (room and filling line)**" also extends to the locations or room or rooms in which the terminal sterilization is performed because each such is a "**sterile processing area**" of a different type.

Based on the preceding, there is no need to make the change suggested.

"Section V.A. Manufacturer
Line 711 requests the e-mail address of the contact person at the manufacturing site. Please clarify the purpose of the email address. In many cases, we do not believe, that e-mail is an appropriate medium for notification of a pre-approval inspection."

The Agency will need to address this comment

"Section V.B. Batch Formula
Please clarify line 720, 'intended validation batch size' vs. the maximum batch size, especially for solution drug products. Specific batch sizes are validated for manufacturing efficiency and market demand and may not be known at the time of submission."

Again, the Agency should address this comment.

From the reviewer's point of view, since the Agency requires an applicant to be ready for a pre-approval inspection at the time the firm submits its application to the Agency, the firm should know the size of the batch that the applicant intends to validate initially.

In the case of liquids, this size is limited by the working capacity range of the tankage available to the applicant for use by the applicant in the facility designated for the production of the drug product for which approval or license for manufacture is being sought.

Within that range, the applicant is asked to specify a formulation for the size that the applicant intends to perform the firm's initial validation studies for that product.

This request is reasonable because the reviewers' concerns and/or level of concern depend upon the size of the batch.

"Section V.C. Description of Manufacturing Process and Process Controls
Please clarify if the recommendations regarding the BSE statement specified in lines 824-826 are new requirements for NDAs and ANDAs."

Given that BSE and other transmissible spongiform encephalopathies (TSEs) are newly recognized health hazards, the Agency is simply providing a recommended means by which an applicant can provide assurance that producing the product in the facilities specified in the application does <u>not</u> pose a threat to the health of those will take the drug product should the Agency approve the application.

Hopefully, all recognize that demonstrating product safety is <u>not</u> a new requirement.

"Are these recommendations applicable to the Drug Substance and Drug Product?"

As written, these recommendations apply to any ANDA or NDA that a firm submits to the Agency – typically such are submitted for drug products.

However, to the extent that they ensure safety, they should be applied equally to any component, equipment, or facility that may be used in the production of the drug product that is at risk of being contaminated by any TSE.

This is the case because there are no simple tests to detect such contamination and the putative causative agents ("prions") are difficult to destroy.

"The Process Controls section (lines 832-916) is very detailed and requires more information than previous guidances or GMP's require."

While this reviewer would agree that the "Process Controls" section requires more information that previous guidances have required, the recommendations don_ot require more than the **CGMP** regulations (**21 CFR Parts 210** through **226**) clearly require.

In this regard, the reviewer suggests that the commenters carefully review all of **21 CFR Subpart F—Production and Process Controls** and **21 CFR Subpart I—Laboratory Controls** from a "process control" perspective.

All that the current recommendations do is provide a recommended approach that an applicant can use to demonstrate that their proposed processes conform to the clear written requirements set forth in the applicable **CGMP** regulations including, but not limited to, those set forth in **21 CFR 211 Sections 84**, **101**, **110**, **160**, **165**, **167**, and **194**.

"Line 850 should be revised from 'All' process controls to 'Appropriate' process controls per the ICH CTD guidance document."

The requirement enunciated in **Line 850** recommends that a firm comply with the clear written requirements of the drug **CGMP** and recommends this approach to demonstrating the requisite compliance.

Regardless of the recommendations in any ICH guidance, the Agency is compelled to propose guidance for drug products that meets the legally binding requirements set forth in the drug CGMP regulations just as drug manufacturers are required, under penalty of law, to produce their drug products in compliance with all of the applicable requirements of the drug CGMP regulations.

Each party to the ICH guidance is similarly constrained.

"Section VII. Control of Drug Product, A. Specifications
In Table 3, please identify and define the footnoted terms elsewhere in the document so that the footnotes do not need to be repeated."

From an ease of use point of view, it is better to include table footnotes and definitions "in" the table rather than elsewhere even if this requires some of the material to be repeated.

From this reviewer's point of view, the Agency has gotten it right, ease of use is more important than a minor reduction in document size that makes the guidance more difficult to use.

"Section V.II.B. Analytical Procedures
Please clarify that 'Official Compendium' includes other compendia besides the USP."

The **FDC Act** only recognizes the ***United States Pharmacopeia*** ("**USP**"), the ***National Formulary*** ("**NF**") and the ***Homeopathic Pharmacopeia of the United States*** ("**HP-US**") as "official compendia" and none other.

Thus, bound by statute, the **FDA** can only recognize the same as official compendia.

"Section V.II.C. Validation of Analytical Procedures
Please clarify in lines 1276 and 1277 that validation information is not required to be submitted for compendial procedures."

Given the definition, provided in **Lines 1274** through **1276**, for validation of an analytical procedure, **"Validation of an analytical procedure is the process of demonstrating that analytical procedures are suitable for their intended use,"** no such clarification is warranted.

This is the case because 21 CFR 211.194(a)(2), among other things, requires, **"The suitability of all testing methods used shall be verified under actual conditions of use."**

Thus, the guidance conforms to the explicit requirements of the drug **CGMP** and needs no such clarification.

"Line 1278 should be revised to state that stability data, including data from stress studies, 'may' be used to support the validation of the analytical procedures."

The analytical procedures in question need to have their ability to measure the level of the active verified under actual conditions of use and part of that verification requires that the method for each active be specific enough that it is not significantly biased by: **a)** other components and impurities that may be present and **b)** degradants that may form over time.

Thus, the guidance is correct as written – such data **should** be used to support the validation of the method.

"Section V.II.D. Batch Analyses
Please clarify lines 1289 - 1291 to state that batch analyses data 'may' also be provided for other batches. Batch analyses data should not be required for supportive batches including feasibility, process evaluation, formulation studies and batches prepared for registration in other regions."

From the point of view of sound science as well as that of regulatory compliance, specifications must be established and justified based on a body of data that demonstrates that said specifications are scientifically sound and appropriate for compliance with the drug CGMP.

As written, **"Batch analysis data should also be provided for any other batches that are being used to establish or justify specifications and/or evaluate consistency in manufacturing,"** is consistent with the drug CGMP and needs no change.

If an applicant feels that data from some batches need not be included, then it is their right, *subject to inspectional review and the penalty of law*, to omit any batch analysis or other data that they choose from their application.

After all, guidance is just that guidance and not regulation.

Therefore, this reviewer must, for the reasons stated, also object to the change proposed.

"Section VILE. Characterization of Impurities
The list of expected impurities is inconsistent with the ICH guidance on Impurities in New Drug Products. Leachables from the container closure system are not included as impurities per this ICH guidance."

Again, ICH guidance is not law.

It does not override *sound science* or the requirements set forth in the drug CGMP.

Since "leachables" from container closure systems and labeling have been and are a recognized problem that has: **a)**, in more than one recent instance, adversely affected product safety and **b)** repeatedly led to product recalls, it is appropriate that the Agency include them as "impurities" in the drug product that a firm's application should address.

Based on the Agency's findings, one would hope that the ICH guidelines will soon be appropriately revised to address what is obviously a product contamination and product safety issue.

"Section X.C. Stability Data
Please clarify lines 1570-1571 by defining 'stability study report' because this may not be common terminology across the industry."

Based on this reviewer's experience and interactions with colleagues from other firms in the pharmaceutical and chemical industry, most understand what a "**stability study report**" is though they differ on exactly what information must be included therein.

Linguistically, in the context used the definition seems to be almost self evident, any report generated by the stability studies being addressed.

If the applicant does not formally summarize the stability data into written stability reports, then that firm can simply submit the appropriate portions of the **CGMP**-mandated laboratory record (**21 CFR 211.194**) that is required by **Subsection (e)** to be maintained for each stability test.

"Section X.C.3 Stress Studies
Please clarify lines 1617-1618, to state that results from drug product stress testing and thermal cycling should be provided if used to support the product's labeled storage statement."

This reviewer disagrees; all are requested and all should be because they serve the other purposes stated in **Lines 1617 – 1622**.