Guidance Line #	Proposed Revision	Rationale
956	Remove "documentation" from "Description, documentation, and results". This reviewer is opposed to this change.	Documentation is a PAI inspection item not a filing requirement. First, nowhere in the CGMP regulations or the FDC Act does this reviewer find any prohibition for the Agency's request for an applicant to provide the requested documentation in support of an application and require it to be only reviewable as part of an on-site inspection. **(See also, review in Row "982-983.")** Second, guidance is guidance – not requirement. Third, the documentation requests are justified because they provide the supporting evidence (proof) that the applicant's assertions are valid and/or CGMP compliant. For all three reasons, this proposed change to the draft guidance is not sound and should not be made.
982-983	Delete "and the applicant intends to perform full testing on each batch received,". This change should not be made.	Full or reduced testing by the applicant is a GMP issue, not a registration issue. Contrary to the commenter's remarks, all FDA personnel are charged with ensuring that all manufacturing practices and drug products comply with CGMP. Thus, this is a registration issue because the reviewer is required to ascertain CGMP adherence prior to recommending approval. Moreover, the phrase is a critical conditional limit on when the applicant may simply list the compendial monograph without explanation. For the preceding reasons this comment should be rejected. **(See also, review in Row "956.")**
982	Replace "with no additional testing" with "and no additional testing is needed to ensure the suitability of the excipient in the product". Not only does this reviewer oppose this change he is also concerned because the commenters have distorted the proposal by removing it from its context.	Additional testing is done from time-to-time for a variety of reasons. This section should focus on attributes of the excipient that ensure product quality. While the commenter's first statement is true, it is a "sound bite" that has nothing to do with the context. The second sentence is, at best, a red herring. Factually, the text states (emphasis added), **"Compendial-Non-novel Excipients: [26] 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."** All that the preceding does is address the conditions under which it is appropriate to list under P.4, the excipient without providing detailed information under P.4.1 through P.4.4. Based on the context, the proposed change is irrelevant and, as such, should be rejected.

Guidance Line #	Proposed Revision	Rationale
986-987 &989-990	Delete "The P.4.1 to P.4.4 for each individual excipient should be grouped together in the application." In this instance, the reviewer is of two minds. On one hand, this reviewer sees the utility of a common format. On the other hand, this reviewer recognizes that the Agency isn_ot legally bound by the guidance published by ICH. On balance, this reviewer will leave it up to the Agency to decide which is better.	While this may be useful for the FDA, it is inconsistent with the organization of the CTD guideline and granularity document. If FDA disagrees with the organization of CTD it should work through ICH. While the commenter's first statement is true, it ignores the reality that the guidance issued by the ICH is, just that, guidance does not legally bind the FDA. However, this reviewer was unaware that these commenters have standing to suggest the FDA's course of action*vis- à-vis* its interactions with international agencies – this reviewer thought that such fall within the province of the ***United States Congress.*** If this reviewer is incorrect, hopefully, the commenters will provide the statutory language that binds the Agency to follow ICH guidances even when they conflict with US statutes or regulations.
991	Delete the comment "Additional CMC information can be warranted..." or provide an explanation of the type of details that can be warranted. The reviewer objects to this comment, as it decontextualizes and misquotes the text but would welcome the Agency providing added text to assist the applicant in understanding what is required.	Clarity. Would that the commenters were equally concerned about accuracy. The unmangled text (Lines 990 – 991) states: **"Furthermore, depending on the circumstances, additional CMC information for the excipient can be warranted."** Moreover, because the comment ends with "warranted..." the commenters are recommending removing the rest of the following text associated with this text. Since the Agency's observation is a valid one, hopefully, the Agency will honor this commenter's request and provide more detail here.

1022-1030	Delete this paragraph. This reviewer knows that this paragraph should be retained and the Agency's request is rational and measured. The text for lines 1022 – 1030 should remain: "In addition to listing all the tests for an excipient, the specification should 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).[27] At a 1024 minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1)). However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities, and the specification should include testing for potential impurities and contaminants for each batch received by the drug product manufacturer.	1. Full testing must be done by either the manufacturer of the excipient or the applicant. However, the issue of the applicant doing full testing or reduced testing is a GMP issue and shouldn't be specified in the application. 2. If FDA wants to make a policy statement of specifications and testing for polyols, it should do that independently of the drug product guideline. **Re: Commenter's "1."** The FDA does not require the manufacturer of an excipient, especially foreign manufacturers, to perform full **USP-NF** testing on excipients nor does it routinely inspect such; and the **USP**, in its **General Notices**, does not require the manufacturer of any component to do any, much less all, of the compendial tests for batch release. Thus, there is no assurance that the manufacturer of the excipient does full compendial testing or any compendial testing on each batch of each excipient that said excipient manufacturer sells. Unless the applicant commits to and spells out what exactly what tests will be done on each shipment of each lot and by whom, there is: **a) No assurance that the requisite testing will be done** and, more important, **b) No assurance that the application provides assurance that the sponsor's sampling and testing plans are CGMP compliance.** Again, the commenters ignore the **FDC Act** that requires **CGMP** compliance of all drugs (substances and products) and compels the **FDA** to ensure that all drugs, and the process and controls appertaining thereto, are **CGMP**-compliant. The Agency should include requests for whatever information it must have to ensure that a proposed drug product and its processes and controls are **CGMP** compliant – it is not limited by law to only obtaining this information, as the commenter's remark indicates, by inspecting the appropriate premises **Re: Commenter's "2."** Contrary to what the commenters state, the text on polyols is ONLY offered in support of the Agency's request for an additional test on each lot where there is a "concern" – in the example the concern is ***safety***. The FDC Act compels the Agency to demand that ***drug safety issues***, including those associated with any excipient, must be properly addressed in the drug manufacturing process and the drug product. Since the existing CGMP incoming controls are crucial to assuring component safety, the Agency's text draft should be kept as it is.

Guidance Line #	Proposed Revision	Rationale
1037-1038	Delete the statement "-or test results will be accepted from the excipient manufacturer's COA". This reviewer disagrees.	If the standard is the monograph standard, then the issue of accepting results from the supplier is a GMP issue. **See** the reviews in **Rows "956," "982-983" and "1022-1030"** on the previous pages as well as those that address the "GMP" issue in prior comments.
1089-1094	Delete this paragraph. This reviewer knows that this paragraph should be retained as it is: "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). Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged."	Comparison of COAs from the manufacturer and the applicant is a GMP issue. Requiring such a comparison in an application is an unjustified new regulatory requirement. Such data/information can be provided upon request during a GMP audit. It should be sufficient to provide a representative COA from the drug product manufacturer which reflects data used for the purpose of establishing specification compliance. Contrary to what the commenters say, no comparison is requested; all that is requested is a copy of the certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer ... for the components described in P.4" for those "materials used to produce the batch described in the executed production record (R.1.P)."– copies of information – NOT comparisons. If, *as the commenters state*, these are GMP issues, then by law, they are **CGMP** issues and the Agency's lawful requests should not only be honored but also supported. (**See also** the reviews in **Row "1022-1030"** on a previous pages as well as those that address the "is GMP" issue in prior reviewer remarks.)
1149	The terms "interim acceptance criteria" and "sunset provisions" should be more clearly This reviewer agrees and suggests that the "Glossary" option should be used.	While these terms are commonly used in some areas, they may not be familiar to all applicants. The addition of definitions defined either here or in the glossary would help in these cases.
1153-1155	Reword to say "if a test that is usually performed on the finished product, are instead performed in-process, the in-process results should be provided in the batch analysis, e.g. assay on a core tablet in lieu of assay on the finished coated tablet. This reviewer disagrees with the proposed rewording of text that the reviewer is clear on the grounds of "Clarity," especially when the commenters' proposal CLEARLY makes the text less clear.	Clarity First, *in context*, the text states: "The specification sheet should also identify: • tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))" All that is requested is for the applicant to identify those tests that can be performed in-process. Second, in context, the proposed text would state: "The specification sheet should also identify: • if a test that is usually performed on the finished product, are instead performed in-process, the in-process results should be provided in the batch analysis, e.g. assay on a core tablet in lieu of assay on the finished coated table" Obviously, the commenters' alternative is, at best, less clear than the draft text.

Guidance Line #	Proposed Revision	Rationale
1156	General descriptor of analytical procedures. Delete rest of the statement starting from " ....identifying which are regulatory .....can be used for a test". This reviewer objects to this change on the grounds that a) it does not add to the application's assurance of compliance and b) the commenters' rationale does not support the change suggested and, indeed, discusses providing this by electronic reference to "method presentations" that contain the requested information.	From the example in Table 3 it appears that what is expected here is an in-house method number. The FDA almost (but not quite) appears to be asking for the in-house specification document. It should be sufficient to give the specification and a general descriptor of the technology applied e.g., Assay, HPLC or Identity, Infrared. An electronic cross reference to the specific method presentation within the submission could be included if necessary. It shouldn't be necessary to distinguish between regulatory and alternate procedures in the specification presentation. This is done as part of the method presentations. As the commenters' rationale states, the requested information is readily available. The request is again just of an annotated list – in this instance for methods (regulatory and other) when there are multiple methods listed for a given test. Based on the preceding, the draft text should remain as it is.
1174	Delete reference to in-house method numbers(e.g., AP #EFG, AP #PQR, etc). Delete Regulatory and alternative method This reviewer objects to this and any proposed change where, as is the case here, the rationale is essentially "we don't want to"	See comments above. Since FDA registrations are being done electronically now, a cross reference to where the method appears in the submission can be provided. In-house identifiers differentiation for methods should not be part of the regulatory commitment. None of the comments present any science-based or regulatory-based rationale from these commenters who claim to support "proposed revisions" with "rationale."
1208-1221	Delete. This reviewer opposes with this deletion, and recommends the text should be changed as follows: • **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**	This amounts to a commitment to operate in accordance with cGMP. Since our operations are fully expected to be GMP compliant, such a commitment statement should not be necessary in a regulatory submission. Because PQIT is beyond (*in addition to*) the **CGMP** minimums, a firm wishing to implement a PQIT must make such a commitment or the **FDA** cannot use said PQIT in determining whether or not to recommend application approval. Moreover, any truly **CGMP** compliant manufacturer wishing to use the PQIT approach should have recognized the reality of this reviewer's previous observation and would 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. For all of the preceding reasons, the unchanged draft text, or better, should be included in the final guidance.

Guidance Line #	Proposed Revision	Rationale
1288	Change to read "Batch analysis data should be provided for all relevant batches used for...". This reviewer objects to this change and would propose the following as a ***scientifically sound*** and ***appropriate***, CGMP-compliant alternative for **Lines 1288 – 1291**: "**Batch analysis data should be provided for all batches used** in studies conducted to assess clinical efficacy and safety, bioavailability, bioequivalence, and primary stability."	Need to avoid the implication that every clinical or developmental batch needs to be reported. All studies and/or batches may not be relevant to the application, for example exploratory studies on other indications. As an investigator having in-depth experience in investigating production process for the root causes of the differences between batches and the factors that affect or correlate with drug-product batch values, the requested information is crucial to determining whether or not a process and the controls on it are **a)** operating in compliance with **CGMP** and **b)** capable of producing batches of drug product that are sufficiently defined and controlled to the point that the data obtained predict that all of the units in the batch would, if tested, pass. In addition, as written, this reviewer's change avoids the commenters' first concern ("the implication that every clinical or developmental batch needs to be reported"). Since the commenters' second sentence did not address or provide any support for any other change, this reviewer can properly ignore it. Further, by making the change in the manner proposed by the reviewer, this reviewer avoids introducing the obvious ambiguity that inserting the word "relevant" would create. Based on the preceding, this reviewer knows that the commenters' expressed concern has been addressed without introducing the unneeded ambiguity that the commenters' change would have introduced. The reviewer's proposed alternative should be incorporated into the final guidance.

Guidance Line #	Proposed Revision	Rationale
1291-2	Change to read "The batch analysis tabulation should include a description of the batches.".	It should be more efficient for the chemical reviewer to assess data tabulation than a pile of COAs. Having both COAs and collated data is unnecessary and provides no added value to the intended purpose of batch analysis data.
	This reviewer opposes the changes proposed by the commenters and, for the reasons stated, thinks that the draft text, "**The batch analysis reports (e.g., COAs) and collated batch analyses data should include a description of the batches,**" should be incorporated "as is" into the final guidance.	This reviewer disagrees with the commenters' broad generalization concerning COAs, "tabulation" (collation) of data, and review efficiency. Factually, COAs are not requested *per se*, they are but one example of what can be used for the batch analysis reports requested. Second, which is needed depends upon what the reviewer's concerns are and, since the Agency that has the relevant review experience request is making this request, this reviewer must defer to theirjudgm ent of what is needed for the efficient review of an application. Third, reviewers other than "chemical reviewers" do review this information. Fourth, the batch analysis reports, when structured as the Agency requests, do provide significant relevant information beyond the data. Finally, the commenters' last remark is empty rhetoric from a speaker that is obviously opposed to providing the information requested.
1292 and 1328-1332	Delete the word "collated" and replace by "tabulated". This reviewer objects to the proposed change because **a)** the change is unwarranted and **b)** the commenters supporting rationale is not valid. (**See also Row** "1291-2")	Clarity First of all, changing one word that has the same denotative meaning and similar connotative meaning as another word with that other word may add clarity. However replacing one word with another that has a similar but different meaning does NOT add clarity, it changes the meaning. While tabulated information is a collection arranged in a list or table, collated information is a collection of information (data) arranged in a manner that aligns the values from similar but disparate instances of the collection. Inspite of the commenters' using the terms interchangeably, they are not the same. Therefore, the rationale proposed is not supported factually. Moreover, it would seem to this reviewer that these commenters use "Clarify" whenever these commenters are at a loss to present any meaningful rationale for what they propose.

Guidance Line #	Proposed Revision	Rationale
1311-15	Delete the requirement for Batch Analysis Reports, This reviewer objects to this change.	A well designed tabulation of data should suffice. This reviewer's objections are based on: a) The rationales previously stated in the reviewer's prior remarks (**see table rows** "1288" and "1291-2"), and b) The fact that the commenters do not present a rationale that is supported by as much as a reference to an logical exposition based on sound science, regulatory requirements, or even on some practical experience by the commenters – all that is presented is a statement that doesn't even include what the commenters would consider a *well-designed* "tabulation of the data" that, in the commenters' view, "should suffice."
1343-1346	Revise to say "Potential drug-product impurities should be listed. These should include degradation products of the active ingredient, and residual solvents. For some combinations of drug, dosage form, and route of administration, enantiomeric impurities, excipient degradants, and/or leachables from the container closure system may also need to be considered. For the reasons stated, this reviewer opposes the commenters' proposed changes and thinks that the draft language should be incorporated "as is" into the final CMC guidance as: **"All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification."**	Not all of the listed sources of impurities are relevant in all cases. In general it serves little purpose to discuss well known excipient degradation products for a solid oral dosage form. Notification that the applicant should consider other sources of impurities in specific instances should be sufficient. First, this reviewer agrees with the commenters, "Not all of the listed sources of impurities are relevant in all cases." Thus, this reviewer was perplexed to see that the commenters proposed to change the word "expected" to "potential" even if the scope of the request were restricted to the drug product. The commenters' second remark is a generalization that adds little to support the change proposed. In the third statement, the commenters' remark seems to go against the industry's position that applications be treated uniformly because it suggests that each reviewer or review team should decide the scope – an approach certain to lead to variable levels of concern. Moreover, the proposed changes would also, if adopted, lead to ambiguity and variable review outcomes for, in the case of ANDAs, submissions for the same drug products submitted in different years. The Agency's request seems much more likely to result in improving application uniformity, application review uniformity, and facilitated application review than the commenters' alternatives.
1346-1349	Delete "drug substance process impurities...". This reviewer disagrees and thinks that the current language (that only requires listing them) should be retained or, failing that, cross-referenced to their listing PROVIDED that listing is in the CMC section of an application.	This section should focus on impurities unique to the drug product. Since any drug substance process impurities probably also be present in the drug product, a cross reference to drug substance impurity information should suffice. **It shouldn't be necessary to discuss it again as part of the drug product impurity discussion.** This reviewer finds the commenters' remarks unconvincing and/or distortive (e.g., turning a request for a list into one for a discussion).

Guidance Line #	Proposed Revision	Rationale
1362	Regarding identification of impurities, the information provided should include structural formula, empirical formula, molecular weight if not provided in S.3.2. Providing the structural elucidation for all potential impurities and degradants should not be necessary. This reviewer disagrees with the commenters' position and thinks that the draft text should be kept as it is.	For those situations where there are (for example) in excess of twenty **potential** impurities in a drug substance, this could prove really burdensome and result in an entire volume just for impurity structural elucidation. The companies should be left to determine the best approach to providing what is most pertinent and meaningful for the submission. Since the draft text only requests information on expected impurities (those expected in the components) and, after manufacturing, in the drug product –n ot all potential ones, this reviewer thinks that the number in most cases will be less than half of what the commenters suggest. Moreover, the manufacturer, by using purer components when such are available, can minimize that number in most cases to only a few such.
1457	Sunset test protocol - provide further clarification. This reviewer concurs.	This is a good approach and should stay in the Guidance. It would be helpful if the Agency can further define expectations related to this protocol.
1480	Interim acceptance criteria – provide further clarification. This reviewer concurs.	This is a good approach and should stay in the guidance. It would be helpful if the Agency can further define expectations with respect to interim specifications, i.e., what type of submission would be required to finalize the specifications. Also, are these interim specifications applicable to applicable to in-process testing as well?
1570-1571	Delete "Stability study reports should also be included." For the reasons stated, this reviewer thinks that the draft text should be retained.	This assumes that freestanding stability studies reports are written. The guidance should also describe the information needed in the application, and allow flexibility in the format. While the commenters are free to infer that the draft language presupposes "freestanding stability study reports," the text does not make that request – therefore the first statement in not factual. The second statement seems to be, at best, misplaced.
1573-1593	Move the section on analytical procedures after the section on stress studies (1622). This reviewer concurs.	This material applies to formal, supporting, and stress studies and would be better as a separate section.

Guidance Line #	Proposed Revision	Rationale
1580	Delete: e.g. weight loss". For the reasons stated, this reviewer does <u>not</u> agree with simply omitting the example. However, this reviewer would suggest that the Agency could choose a different test as its example.	Determination of weight loss change with a calibrated balance is a standard laboratory procedure and should not require presentation of the procedure and validation data. Factually, based on experience in more than a dozen US and foreign laboratories, there is no one standardized procedure that all laboratories use nor, for that matter, a uniform calibration procedure for the balances used or uniform balances types. As a Ph.D. Analytical Chemist and former Quality Control director overseeing the operation of the internal RM, Validation, In-process, Release, Stability, Complaint and method's improvement and validation lab functions as well as several specialized contract labs, having worked with the lab operations in more than a dozen other firms in the United States, United Kingdom, Japan, Germany, France and China, this reviewer can attest to the need for labs to have and the Agency to request proof of the reliability of even the simplest unit operations.
1607-1613	Delete the material starting with "Stability data to support holding..." to the end of the paragraph. This reviewer strongly opposes this deletion for all of the reasons stated – the draft text, or, if such exists, an improved version thereof should be incorporated into this final CMC guidance. [**Note:** Lacking the data requested, an application reviewer <u>cannot</u> ***know*** that the holding times proposed in an application are scientifically sound and appropriate – a **CGMP** requirement. *If these holding times are <u>not</u> substantiated by the data provided*, then, the prudent application reviewer could place the application on hold and request the applicant provide said data. *Most firms claim they do <u>not</u> want to delay their applications.* If this is the case,*p rudent firms will report the stability data that support any and all hold times <u>not</u> just those longer than 30 days.* Finally, *because this document is guidance*, a firm may choose to follow the course that these commenters have proposed instead of the one the Agency has proposed.]	1. In-house holding of in-process materials should be considered a GMP requirement, not part of the application. 2. This is not "supporting studies" as defined by ICH Q1A. Contrary to the position stated by the commenters in **Point 1**, in addition to the drug product ("finished dosage form"), the Agency is charged with evaluating whether or not the production processes and controls do, or do <u>not</u>, comply with **CGMP**. Apparently the commenters have overlooked the specific requirements that address the issue the commenters raise. The applicable section is **Sec. 211.111 Time limitations on production** states (emphasis added): **"When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented."** Thus, while the applicant is required to establish time limits for the completion of each phase whether that limit is one day, one week, one month or longer. The Agency recognizing the burden that supplying all of the required studies would impose has judiciously limited their request to a hold period of 30 days or longer." Thus, the request is very reasonable. Moreover, were it to be removed, each application would be subject to the judgment of the application reviewers as to what the *"time-delay start point"* should be for requesting such studies – *silly me, thought the industry was for uniform reviews.*

Guidance Line #	Proposed Revision	Rationale
1651	Delete the footnote, or revise to say the ICH stability guidelines are the primary reference sources. This reviewer disagrees with the commenters' remarks.	Regulators and industry have worked very hard to develop the ICH guidelines. FDA guidelines should not supersede them. FDA guidelines are only appropriate to address areas not covered by the ICH or unique to the U.S. First, if the Agency were to issue guidelines, they would supersede any guidance – because they are legally binding on both the industry and the Agency, the FDA does not currently issue guidelines, Knowing that the FDA understands better than this reviewer what itcan and should do with respect to the ICH guidances, this reviewer will defer to their judgment and, barring an Agency-initiated change, this text should be left as it is in the final CMC guidance.
1793	Delete "Phase III Clinical" from the sentence. The concept of providing representative EPRs is good and should be retained.	The regulations require that EPRs be provided for bio-availability, bioequivalence and primary stability lots. The provision of EPRs for multiple stability lots, for example, adds bulk and complexity, but may not always serve a useful purpose.
1811-1816	Delete • Name and address of DS manufacturing • Names and addresses of sources of noncompendial excipients • Names and addresses of sources of container-closure system for DP • Names and address of each contract facility This reviewer disagrees with this unless the information is requested elsewhere in the CMC section of the application.	All of these pieces of information are included elsewhere in the registration and should not need to be repeated here. In the interest of facilitating any future updates, it would be important to simplify by only stating the information once in the appropriate place within the appropriate section. Because the CMC section is the only section provided to the Agency inspectorate and that inspectorate needs this information for site evaluation and scheduling purposes especially in instances where the source is, as it increasingly, a foreign source. However, given the size of an application and the need to partition it among various review groups, as long as physical copies are permitted the CMC guidance may, for the reasons cited, and other sections may need to contain information in multiple locations to facilitate the review process. In such cases, the goal of review facilitation should continue to supersede the goal of "ONLY in one location" simplification.
1817 -1819	Delete the sentence that starts " This should include...". This reviewer knows that this draft text or, should it come to exist, an improved version thereof should be incorporated into the final CMC guidance.	Provision of duplicate CofAs is unnecessary. Comparison of supplier and applicant data is a GMP issue and can be addressed by the inspector if appropriate. While this reviewer agrees that providing "duplicate CofAs is unnecessary," this text makes no such request. Since the Agency is charged with a duty to ensure that the manufacturing, controls, and drug products are **CGMP** compliant, and the commenters admit that this comparison "is a GMP issue" that "can be addressed by the inspector," then it is also an application review issue that can be addressed by requesting the applicant to provide the requisite information.

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

Aventis Pharmaceutical's Submission Posted June 25, 2003 To Docket 02D-0526: "C-05"

Note: The original INTRODUCTORY 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. In this review, this reviewer's comments are made after the commenters' comments and placed within the text box containing the commenters' comments.]

This commenters begins by stating "Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled 'Drug Product: Chemistry, Manufacturing and Controls Information'. This draft 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). This draft guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format. We offer the following comments/clarification for your consideration.

"General Issues"

"For clarity and consistency, please consider the following comments:

- Since there is heavy emphasis on excipients, especially novel excipients in Section IV. PHARMACEUTICAL DEVELOPMENT (P.2) - Part P.2.1.2, specifications for novel excipients should also be listed in Section VI. CONTROL OF EXCIPIENTS (P.4) - Part P.4.6 and in Section XI. APPENDICIES (A) – Part A.3.
- 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 interests of "harmonization," suggests that the CTD style be used throughout.

"Section II. BACKGROUND
Part B. Content Information Included in an Application
Page 5, Lines 161-163"

"If information is not provided in a P subsection at all or for a particular product presentation or manufacturing scheme, this should be stated in the application and a reason given."

"We suggest adding clarification to confirm that the statement, and corresponding rationale, for not providing information for a P subsection should immediately follow the relevant section/subsection number."

This reviewer concurs.

"Section IV. PHARMACEUTICAL DEVELOPMENT (P.2)
Part A. Components of the Drug Product (P.2.1)
No. 1. Drug Substance (P.2.1.1), a. Key Physiochemical Characteristics
Page 11, Lines 383-386"

"Key physiochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic form, solvation or hydration state, pH, dissociation constant (PKa)) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed."

"We suggest replacing curved brackets "( )" with square brackets "[ ]" since a subset is included within the sentence."

While this reviewer concurs, what is being suggested would be clearer if this comment were reworded to state, for example:
"We suggest replacing the inner set of curved brackets '( )' with square brackets '[ ]' since a subset is included within the sentence."

Section V. MANUFACTURE (P.3)
Part A. Manufacturer(s) (P.3.1)
Page 18, Lines 688-689 and Footnote 19
Page 19, Lines 695-697 and Lines 710-712

"Each site should be identified by the street address, city state, and when available, the drug establishment registration number.[19]

Footnote "[19] – See 21 CFR part 207 for registration requirements for producers of drugs. The registration number is the seven-digit central file number (CFN) or ten-digit FDA Establishment Identifier (FEI)."

"Addresses for foreign sites should be provided in comparable detail, and the name, address and phone number of the U.S. agent for each foreign drug establishment as required under 21 CFR 207.40(c), should be included."

"To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail addresses of a contact person be provided for each site listed in the application."

"Should full establishment information be included in both the body of the application and the Form FDA 356h?"

Because only the CMC section of the application is provided to and used by the FDA inspectorate in contacting sites, scheduling the site inspections, and PAI audit-related activities, providing this information within the body of the application will expedite this phase of the review. This is especially important when the site is located in a foreign country.

Section V. MANUFACTURE (P.3)
Part C. Batch Formula (P.3.2)
No. 1. Flow Diagram
Page 22, Lines 790-796

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)

"We suggest that a more precise definition of "noncontinuous process" be included in this section. 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 agrees with commenters' remarks but would recommend using the term "discontinuous process" as the definition basis.

"Section V. MANUFACTURE (P.3)
Part C. Batch Formula (P.3.2)
No. 3. Reprocessing and Reworking
Page 24-25, Lines 887-912"

"Reprocessing is the introduction of an in-process material or drug product, including one that does not conform to a standard or specification, back into the process and repeating steps that are part of the approved manufacturing process. Continuation of a process step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing. For most drug products, reprocessing need not be described in the application. In general, the documentation of and data to support the reprocessing of a production batch should be retained by the manufacturer and be available for review by FDA upon request. However, if there is a significant

potential for the reprocessing operation to adversely affect the identity, strength, quality, purity, or potency of the drug product, the reprocessing operations should be described and justified in this section (P.3.3) of the application. For example, reprocessing of proteins would be considered a reprocessing operation that should be described in the application. Any data to support a justification should be either referenced or submitted in P.3.3. However, validation data, when warranted to support the reprocessing operation, should be provided in P.3.5.

Reworking is subjecting an in-process material or drug product that does not conform to a standard or specification to one or more processing steps that are different from the manufacturing process described in the application to obtain acceptable quality in-process material or drug product. In general, reworking operations are developed post approval, and the application is updated through submission of a prior approval supplement. However, if reworking operations are anticipated at the time of original submission, they should be described in this section of the application (P.3.3) with justification for the reworking operation and any data (or references to data) to support the justification. Validation data, when warranted to support the reworking operation, should be provided in P.3.5."

"Although narrative definitions are given for reprocessing and reworking in this section, the Glossary contains no definitions for these terms. We suggest adding these terms to the Glossary."

This reviewer agrees

Section V. MANUFACTURE (P.3)
Part D. Controls of Critical Steps and Intermediates (P.3.4)
Page 25, Lines 920-930

"In this section of the application, all critical process controls (see section VC.2) and their associated numeric ranges, limits, or acceptance criteria 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."

"We suggest adding a provision in this section for applicants to include justification for providing interim specifications for product release. This suggestion is based on the understanding that, for most new drug products, there may **be** limited historical data for in-process or final release specifications at the time of submission. With the addition of this provision, an applicant could commit to introduce finalized specifications in a post approval submission."

This reviewer agrees with the commenters' proposal but would suggest that the text in the supporting statement be corrected to make it grammatically correct.

Section V. MANUFACTURE (P.3)

Part D. Controls of Critical Steps and Intermediates (P.3.4)
Page 25, Lines 932-935
• Biological Tests

Analytical Procedures and associated validation information should be provided for biological tests.[23]

"There is no reference provided in this bullet point to refer the applicant to appropriate guidances for establishing acceptance limits for biological tests. Several guidances, points to consider and compendia have suggestions on how to establish fiducial limits, particularly for biological potency assays, which inherently have higher variability (CVS)."

Agreed.

Section VI. CONTROL OF EXCIPIENTS (P.4)
Page 27, Lines 991-995
• Noncompendial-Non-novel Excipients

When warranted, the additional CMC information or a cross -reference to a DMF that provides the additional CMC information should be included in A.3. See sections IV.B.2 and XI.C for additional guidance on the information that should be submitted to support the use of this type of excipient.

-AND-

Section XI. APPENDICES (A)
Part C. Excipients (A.3)
Page 49, Lines 1765-1769
• Other Excipients

Depending on the functionality (e.g., complexing agent) and the route of administration of the drug product, additional information, up to and including the level of information recommended for novel excipients, can be warranted for noncompendial-non-novel excipients. The additional CMC information or a cross-reference to a DMF that provides the additional CA4C information should be included in A.3.

"Advice regarding the content and location of information on non-compendial-non-novel excipients is provided in different sections of this guidance and appears to be inconsistent. Why should "additional CMC information be included in A.3", the CTD appendix for Novel Excipients, when an excipient is by definition "non-novel" (e.g. flavor, colorant, etc.)?"

This reviewer agrees with the commenters' inconsistency remark.
However, even a flavor or a colorant can be "novel" if its has never been used at the level or in the type of formulation in the formulation being submitted,
Therefore, this reviewer respectfully disagrees with the commenters' "by definition" remarks.

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part A. Specification(s) (P.5.1)
Page 32, Lines 1153-1 155

- Tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))

"We suggest adding text to this section clarifying how "tests performed in-process in lieu of finished product testing" should be reported on a Certificate of Analysis - especially for extensive in-process results such as PAT generated data."

This reviewer recognizes that including such guidance would be a good idea but thinks that 1) it would be more appropriate to place it elsewhere and 2) the guidance should be more general to address batch analysis formats other than that of the Certificate of Analysis.

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part D. Batch Analyses (P.5.4)
Page 37, Lines 1297

- Batch identity (i.e., batch number), strength, and size

We suggest including "formulation number" in the list to cover formulation changes during development.

In principle, this reviewer agrees but would suggest that the language be changed to "formulation identifier."

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part E. Characterization of Impurities (P.5.5)
No. 1. List of Expected Impurities
Page 38, Lines 1343-1346

All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification.

Since "Miscellaneous Drug Product Impurities" is defined later in this section (Lines 1393-1409), we suggest that the impurities listed initial in Lines 1343-1346 should include miscellaneous drug product impurities.

For Example: "*All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, and miscellaneous drug product impurities such as excipient degradants ...*"

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part E. Characterization of Impurities (P.5.5)
No. 2. Identification of Impurities
Page 39, Lines 1379-1380

When identification is warranted, the recommendations in S.3.2 of the forthcoming drug substance guidance on approaches for identifying impurities are applicable.

It is difficult to comment on "recommendations from a forthcoming guidance". We suggest that all referenced text be included in the draft guidance that is being reviewed, (i.e., reference only those guidances that can be accessed).

In general, this reviewer concurs with the commenters' remarks.

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part E. Characterization of Impurities (P.5.5)
No. 2. Identification of Impurities
Page 39, Lines 1395-1398

For purposes of this guidance, a miscellaneous drug product impurity other than (1) a degradation product, (2) a residual solvent, or (3) an extraneous contaminant that is more appropriately addressed as a good manufacturing practices issue (e.g., metal shavings).

We suggest adding "extraneous contaminant" to the definition list.

Agreed.

Section IX. CONTAINER CLOSURE SYSTEM (P.7)
Page 43, Lines 1531-1537

A description of the container closure system for the drug product should be provided, including the identity of materials of construction of each primary packaging component and its specification. 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.

We suggest including the container closure system for the proposed marketed drug product in this section.

This reviewer concurs.

Section X. STABILITY (P.8)
Page 44, Line 1546

Information relating to the stability of the drug product should be provided in P.8.

We suggest including a statement in this section (P.8) indicating that stability testing of the drug product should be conducted using the final container closure systems that are proposed in the market application.

This reviewer agrees with this suggestion.

Section XI. APPENDICES (A)
Part C. Excipients (A.3)
Page 49, Line 1748-1751

The chemistry, manufacturing, and controls information for a novel excipient should be provided in the same level of detail and in the same format as the information provided for a drug substance (see the forthcoming substance guidance).

We suggest removing the reference to the "forthcoming drug substance guidance", as it does not yet exist.

Agreed.

ATTACHMENT 1
Drug Product Specification, Test Recommendations for Specific Dosage Forms
Page 54, Line 1964

- Uniformity of Dosage Units

We suggest that the bullet point for this item be properly indented to be consistent with the other bullet points in this section.

Agreed.

GLOSSARY
Pages 58-61

We suggest adding the following list of terms to the Glossary section:
Adventitious Agents
Batch Analysis Data
Certificate of Analysis
Comparability Testing
Compatibility Testing
Compendial Excipient
Executed Batch Record
Non-compendial Excipient
Novel Excipient
Reference Standard
Reprocessing
Reworking
Sunset Testing
Validation

This reviewer concurs but would suggest also adding the following terms:
DMF Standard
Report of Analysis (and, to be in synch with the CGMP regulations use this term in place of or with the phrase "Certificate of Analysis")
Secondary Standard
Verification

Jerussi Consulting's Submission Posted June 25, 2003 To Docket 02D-0526: "C-04"

Note: The original INTRODUCTORY 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. In this review, this reviewer's numbered comments are simply made after the commenter's remarks.

This commenter begin by stating, "I wish to comment on FDA's draft Guidance for Industry - Drug Product - Chemistry, Manufacturing, and Controls Information which was published on January 28,2003 in the Federal Register with comments due by June 27,2003. My comments are attached. This document is well written and is clear and not confusing. It also makes many references to ICH and FDA guidances and to appropriate sections of the Common Technical Document (CTD) whose format is followed. However, I think that the document is too long in that it contains too much "how to" detail and can be shortened by at least one quarter."

"In addition, it requires firms to submit more information than currently for both NDAs and ANDAs since the CTD requires information not previously submitted in drug applications in the United States."

1. This reviewer does not understand the point of this comment.

"Since the CTD format is not absolutely required in the United States (it is "highly recommended" – presentation by Justina Molzon, ICH Public Meeting at FDA, January 21,2003) why would firms elect to submit applications in this format unless they plan to submit also in one or both of the other areas involved in the ICH process (Europe and Japan)?"

2. As with most questions, the answer is because: **a)**, *if nothing else*, doing what is requested has been "highly recommended" by those who review said applications is usually a good idea and **b)**, *as the commenter observes*, it facilitates submission in multiple venues.

"Additionally, since Japan's CTD effort will not cover generic products (presentation by Christelle Anquez, ICH Public Meeting at FDA, January 2 1,2003) the incentive for filing in the ICH areas is reduced thus negating any advantage that the CTD format may have."

3. This reviewer disagrees and would ask the commenter to reread his own prior comment and to consider that many NDAs are filed.

"Since the CTD only involves format, not data, it is also my concern that FDA will require more data in each section than its EU and Japanese partners."

4. Unlike this commenter, this reviewer's concern is that the EU and Japan may require more data than the United States draft guidance proposes.

"Although I would prefer to see the CTD modified and changed, the comments that follow take the CTD as is with no expectation that it may be changed or shortened. Thus, these comments are made in the hope of modifying FDA's interpretation of the CTD and assisting it in finding ways to shorten the guidance."

5. This reviewer is all for comments that more concisely address regulatory requirements and the compliance with the **FDC Act**.

   Moreover, this reviewer tends to dismiss any comment that suggests shortening any document unless the commenter can provide a sound rationale for the shortening and/or provides a clear alternative that ensures that each drug application will contain sufficient cogent information to establish that, if approved or licensed by the **United States FDA**, the CMC portion of the application establishes full **CGMP (21 U.S.C. 351(a)(2)(B))** compliance for "**the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.**"

   As the commenter should well know, failure to comply with **CGMP** adulterates the drug product and makes it is illegal for the manufacturer thereof to offer for sale or such sell adulterated drug products.

   Similarly, it is equally inappropriate for the Agency to approve an application that fails to establish that methods, facilities, controls presented in the application for the drug product comply with CGMP with respect to the manufacture, processing, packing, or holding of a drug product including the packaging, labeling, testing, and quality control of the drug product **(21 CFR 210.3(b)(12))**.

   While other commenters have proposed renaming the "Chemistry, Manufacturing, and Controls" section of an application the "Quality" section, it should be renamed the "CGMP Quality" section if renaming is appropriate because that is what it truly addresses.

   Based on the preceding, this reviewer, as any other interested in **CGMP** compliance, can only support changes that: **a)** do not interfere with an application reviewer's ability to determine whether or not the application establishes **CGMP** compliance and/or **b)** improve application transparency *vis-à-vis* **CGMP** compliance.

"Two avenues are pointed out, one is where the areas that involve an increase of requirements compared to presently submitted drug applications and the other where the document may be shortened without deleting the areas containing substantive matters. The CTD M4Q contains a Module 2, Quality Overall Summary which is not addressed in this guidance. Yet much of the information required in Module 2, Quality Overall Summary is redundant and the document itself states that some of it may be incorporated directly from Module 3. We also believe that Module 2, Quality Overall Summary can be confusing to firms who choose to submit an application in the CTD format and no mention of it and its redundancy in this guidance is an error.

6. This reviewer does not understand what purpose this harangue about "Module 2" has to do with the CMC guidance and would point out that adding verbiage to discuss it would increase the length – something the commenter has stated the commenter is opposed to doing.

"It does seem that with all the information that is suggested to be submitted in Module 3 Drug Product, that Module 2, Quality Overall Summary could be eliminated. However, again, I take it as is."

"Areas where more information is required then under current requirements:

1. Lines 362 - 678 IV. Pharmaceutical Development (P.2), [7.5 pages, 14% of the entire guidance].

This report has not been previously required in an NDA or ANDA. Lines 364 - 367 lists 'information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application' that an application should contain."

7. This reviewer agrees, and is pleased to see that **a)** the Agency has recognized this major deficiency in the previous guidance and **b)** addressed it.

"The guidance then covers 300 lines (377 - 678) to describe specifics about the information that should be included. The recommendation to submit this great amount of information, if followed, will make such a report not only large but time consuming to prepare by a firm and to review by FDA. And for what purpose?"

8. This reviewer recommends that the commenter reread **Reviewer's 5**.

"Some general questions concerning ANDAs come immediately to mind. What kind of a report will a foreign firm submit who has had the product on the market in its own country or in Europe for ten years and has made a number of changes since the product was developed.?"

9. This reviewer hopes that it will be one that complies with the CMC guidance and provide a historical report that addresses the development of that drug product from its beginning up to the present.

"What kind of a report will an American firm make who has had a product on the American market but is now required by FDA to submit an abbreviated application such as recently happened with Thyroxin?"

10. Ignoring the Thyroxin example cited (because it has more to do with the FDA's forcing the innovator to choose: **a)** file an NDA to bring a manufacturer into compliance or **b)** cease making the product), if an American firm who is the innovator decides to file an ANDA (as some have done) for a "generic product" (because its market exclusivity is about to expire or has expired), then that application should conform to the format suggested in the official guidance and provide sufficient data to establish the proposed application presents a **CGMP**-compliant compilation of the information needed for the Agency review and inspection personnel to recommend application approval.

"Will such firms still have information on the development of their product?"

11. If the firm operates under the purview of the **FDA**, it should have much of the information requested in the draft guidance.

For foreign firms, the answer is "it depends."

" If not what kind of a report will they submit?

12. Whatever, the firm in question and the Agency agree upon is available and should be submitted – the same as is the case today.

"And for what purpose?"

13. The commenter is again asked to read **Reviewer's 5**.

"Some specific comments follow:

A. Lines 394 - 399 indicate that if drug substance particle size is expected to influence dissolution, then drug product testing should be performed to test the appropriateness of acceptance criteria for the drug substance. This seems backward since the key for a generic firm is to develop a formulation with the API particle size as supplied by the vendor."

14. First, contrary to the commenter's assertion, the generic firm is required to develop a drug product that is *bioequivalent* to the innovator's product.

To do this, the generic firm must first determine *if there is a particle size effect for the active or actives* and, *when there is*, the general type of particle size ("as obtained from slow recrystallization," "as obtained from rapid crystallization," "micronized," "agglomerated nanoparticle," *etc.*) and, in more than a few cases, the exact crystalline unit structure or structures of the active or actives in the innovator's product.

Armed with that information, the generic firm must: **a)** find a source that can supply the needed structurally equivalent API or **b)**, in the case of micronized materials for which the only available sources are for the crystalline material, **i)** develop an in-house process for the micronization of the API or APIs, or **ii)** find a subcontractor who can provided the needed operation (in the latter case, the generic firm is required to receive, test, and release the supplied bulk to the processor [micronizer] who, under **CGMP**, performs the micronization and, after inspecting each micronized lot, releasing and ship the micronized API back to the generic firm who must receive, inspect [sample and test] and release the micronized product to the generic firm's manufacturing operations).

All of the preceding needs to be appropriately documented and submitted.

Second, since this guidance applies to NDAs and ANDAs, this reviewer is certain that the commenter knows that firms do the studies alluded to as a part of the product development process else why would so many otherwise stable actives be formulated as "salts"?

"The formulation developed with the particle size of the API will effect dissolution and bioavailability and if the firm can get these to come within the expected or required range using the particle size as delivered by the vendor, what testing must be performed?."

15. If nothing else the manufacturer must test to determine that the particle size distribution of each shipment of each lot of the API is the same as

that of the lot shipments used in the studies alluded to by the commenter as well as, for the initial lots, the other testing in the **USP** monograph (to confirm that the API is **USP** grade) as well as other tests that the source (microbial testing on APIs from fermentation), production process (residual solvents, toxic impurities) or method of holding or shipping (contaminants, product mix-ups, and substitution of counterfeit APIs) may indicate need to be conducted.

"B. Lines 422 - 430 concern excipients and a discussion relative not only to the role of each excipient but to their characteristics that can influence drug product performance. What is required at present is that the role of each excipient be listed. How will a veteran formulator who has been formulating products for 20 - 30 years help his firm answer this?"

16. The obvious answer to this question is that it depends on "who that formulator is" and what he or she understands about how to detect, measure and specify such.

    In some cases, the firm will need to hire someone (employee or consultant) who has the requisite knowledge, training or combination thereof.

"The role of each seems to already do that. The formulator knows how each excipient affects drug product performance and so should the FDA reviewer. "

17. Contrary to what the commenter states about formulators, only some know exactly how each excipient affects drug product performance and even fewer understand how the interactions of the excipients in the formulation with each other and the active combine to affect the performance of the drug product. [**Note:** This reviewer's statement is based on more than twenty years of off again, on again consultations with formulators that cannot cogently even discuss the effects of scale on excipient performance much less explain what the critical interactions are among the excipients and the API or APIs that affect product performance.]

    Moreover, since most **FDA** reviewers are NOT formulators, why does the commenter feel that such reviewers should know more than most formulators seem to know?

"The formulator's job is also how much of each excipient gets put into the formulation to give the desired formulation characteristics. The FDA reviewer probably doesn't have that type of knowledge or skill and it shouldn't be needed to review an application. What is important is that the formulation be presented and if it works, what further discussion is needed? The firm is now bound by the selected formulation. "

18. Now the commenter argues that the **FDA** reviewers do not have the same level of knowledge as the applicant firms' formulators.

    Since the Agency reviewers are scientists, *regardless of their skills as formulators*, the application reviewers should be able, *when such information is provided*, to review this type of information and determine whether or not it is sufficient to support the applicant's claims.

Therefore, the guidance's requests in this area are valid and the applicant should provide the information requested.

"C. Line s 492 - 493 discusses the development of the release mechanism of a modified release product. It seems that this should only be necessary when a novel or patented release system is used such as the GITS system when initially used. For other well known controlled releasing agents this should not be necessary since their mode of affecting release is well known."

19. This reviewer knows that this commenter's remark is specious on its face.

Having been intimately involved with the problems associated with getting lots of **Hydroxypropyl Methylcellulose, USP (Hypromellose, USP)** from DOW that were the same as the lots used in the formulation upon which approval and the **FDA**-accepted specifications were based for a generic 450-mg sustained-release Theophylline, this reviewer can attest that the EXACT mode by which these affect release is NOT known. [**Note:** In the instance cited, even with the complete set of parametric measurements that DOW was able to provide, and the creation of a special grade based on feedback of which lots produced acceptable drug units, the generic firm was forced to receive pre-shipment samples of those three to five lots of DOW's production for the month that matched the DOW criteria (DOW "special grade x"), prepare lab scale batches of each, test *not less than* 24 samples from each lab-scale batch (of about 100 units) in the generic firm's ISO-25 compliant lab, and, *based on the results obtained by that lab,* and authorize DOW to ship those zero to three lots that gave acceptable drug product using the pre-shipment samples (yes, 0 % to 60 % acceptable each month from the few (3 to 5) of the 100s of lots that DOW produces monthly – a very small percentage of DOW's monthly production of lots of **Hydroxypropyl Methylcellulose {Hypromellose}**). So much for the commenter's "their mode of affecting release is well known."]

"D. Lines 537 - 539 states that 'In general, use of an overage of a drug substance to compensate for degradation during the manufacture of a product's shelf life, or to extend the expiration period, is not appropriate.' This statement is basically correct in that overages are not to be used ordinarily. However, this would be improved by adding the following statements. The word "considered" should be added before the word 'appropriate'. The thought should be expanded by the following sentence. 'However, certain important drugs would not be marketable unless overages were used, for example epinephrine solution.'"

20. While this reviewer and the commenter seem to agree in principle that arbitrary overages should be avoided, this reviewer recognizes that such must be included to: **a)** ensure that **21 CFR 101(a)**'s formulation requirement of "**not less than 100 percent of ...,**" **b)** make up for losses during production, **and/or c)** compensate for unavoidable degradation during production and slow degradation in the released drug product unit occurring within the drug product's lifetime.

"E. Lines 662 - 663 mention leachables with reference to footnote 17 which states: 'The level of di-2-ethylhexyl phthalate (DEHP) leaching from polyvinyl chloride containers should be assessed, and appropriate reference to DEHP leaching should be included in the product labeling.' Again, this seems to make labeling requirements more stringent than what is acceptable presently. As far as I can determine,

not all drugs packaged in DEHP specifically in LVPs packaged in polyvinyl chloride containers are required to contain such a reference."

21. The commenter's remarks here seem to ignore the reality that, as time passes, the industry and the Agency may identify, as in this case, a weakness in the drug-product safety controls.

If the commenter was to review the Agency's recalls database, the commenter would find that this problem was only identified recently and, therefore, would not have even thought of, much less addressed, prior to the discovery of this problem.

As with all of life, the Agency's regulatory framework is a living and adaptable framework.

The draft text offered should be incorporated into the final CMC guidance because the problem it addresses is real.

"Shortening the Document

We recommend deletion of the following in the draft guidance:

1. In IV. Pharmaceutical Development (P.2) that lines 377 - 678 be deleted, about 7.5 pages. Allow firms to submit what they believe should be in such a report (section) without instructing them as to what should be therein or providing them with a 'how to' guide. After all, the firms have developed the product and should know it best. Depending on the drug that was developed, there is no reason for such a report to be in the same format or cover identical areas for all drugs."

22. This reviewer disagrees because: **a)** the commenter provides no logically rationale for the deletion that is in keeping with either **i)** the industry's avowed goal of uniform review or **ii)** the Agency's goal of receiving uniform applications that provide proof of compliance to all facets of **CGMP**; and **b)**, *based on this reviewer's experience*, this section is a must.

"2. Delete Attachment 1, lines 1856 - 2116, about 6 pages. Leave it up to the ICH and individual firms to recommend/select specific tests for specific dosage forms such as appear in ICH guidance Q6A for solid and liquid oral drug products and parenteral drug products. As noted in the draft guidance, the universal tests have already be stated in Q6A. Allow firms the responsibility to select specific tests that best describe and control their products without too much rote instruction from FDA."

23. This reviewer finds that the commenter's remarks have little to do with the reporting requests of the Agency – factually, each firm must develop and justify (establish) **scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity."** – these responsibilities cannot be delegated

Contrary to the commenter's first remark, "Leave it up to the ICH and individual firms to recommend/select specific tests for specific dosage forms such as appear in ICH guidance Q6A for solid and liquid oral drug products and parenteral drug products," this responsibility is the firms' alone, it cannot be delegated to the ICH nor does the Agency's

draft guidance, by asking that the applicant report the requested information, in any way usurp that responsibility.

What does the commenter's second remark, "As noted in the draft guidance, the universal tests have already be stated in Q6A," have to do with the inclusion of which tests a firm chooses to do, how they do them and the information that establishes that the firm's choices are *scientifically sound* and *appropriate*?

Nothing that this reviewer can see.

The commenter's third remark, "Allow firms the responsibility to select specific tests that best describe and control their products without too much rote instruction from FDA," is but a restatement of the commenter's first remark and contributes nothing of substance to the discussion concerning what information is requested and how it should be structured.

Based on the reality that the Agency's requests are properly balanced between their need to know and the paperwork burden (after all the firm's are supposed to have almost all of what has been requested if they are truly operating in a **CGMP**-compliant manner so there should be no significant "additional controls" burden) and the commenter's failure to provide any cogent rationale for not providing what is requested, the draft text in Attachment 1 should be retained and, where it can be, enhanced.

3. Delete all references that appear in a number of places in this draft guidance to additional future draft guidances. The latter have no real status at FDA or at least are not supposed to have status and therefore really cannot be factored into this particular draft guidance. This will affect perhaps 10 lines.

24. This reviewer agrees that references to non-existent documents should be removed, but thinks that the Agency would do well to incorporate some specifics from each into the CMC guidance and, by adding, "When published, the guidance in the specific guidance will supersede the general guidance currently being provided," allow the CMC guidance to be finalized and issued irrespective of the future guidances.

"4. Delete Table 1: Example Target Composition Statement and Table 2: Proposed Batch Formula (no line numbers associated with these tables). Will save at a minimum of 1 page. Firms know how to prepare batch formulas and composition statements."

25. This reviewer strongly disagrees because, on more than one occasion, this reviewer has found that the formulations developed for submission and, in some cases, approved, provided drug product batches having, on average, a batch level of active that was less significantly than 100 % (down to 96.5 % in one case) of their label claim or targeted level.

Since the problems occurred in several firms, some firms not only do not know how to prepare CGMP-compliant formulas but they also do not do so.

Therefore, this commenter's proposal should be rejected.

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

Aegis Pharmaceuticals' Submission Dated June 12, 2003 To Docket 02D-0526: "C-03"

Note: The original INTRODUCTORY 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. In this review, this reviewer's numbered comments are simply made after the commenters' remarks.

This commenters begin by stating, "Aegis Pharmaceuticals Inc. submits these comments on the Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing and Controls Information; Availability in response to the Federal Register notice of January 28, 2003. This Draft Guidance addresses the information to be submitted in ANDAs and NDAs for drug products to ensure continued product quality. Recommendations are provided on the information that should be included for (1) description and composition, (2) manufacture, (3) control of excipients, (4) control of the drug product, (5) reference standard materials, (6) container closure systems, and (7) stability. Information is also provided on the type of pharmaceutical development information that should be included in an application submitted in the Common Technical Document (CTD) format."

"Aegis finds this draft guidance an unnecessary escalation of requirements for the submission of ANDAs and NDAs. This escalation is most obvious in the requirements for the Pharmaceutical Development Report (PDR). Currently, the information described in the PDR is reviewed with a FDA investigator during an FDA audit. A drug developer collects this information as the process is being developed and it content and format is specific to the SOPS of the developer. This new requirement for inclusion in the ANDA and NDA and the prescriptive guidelines presented, will burden the Agency and restrict the development activities of the firm."

1. First, this reviewer finds that this commenters' use of the word "escalation" for "increase" is either: **a)** an unfortunate choice or **b)** an indicator of the commenters' predisposition to resist any change in guidance in the CMC section of an application.

   Second, the commenters "vociferously" object to having to file the PDR section on the grounds that, "Currently, the information described in the PDR is reviewed with a FDA investigator during an FDA audit."

   In making this comment, the commenters admit that that "same" burden is currently on the FDA's inspectorate.

   Thus, by requesting that same information to be submitted there will be, *contrary to the implication commenters' remarks*, no additional burden on the Agency.

   In the commenters' words, the burden will just be reapportioned so that the larger review staff will just be relieving some of the reduced inspectorate's burden.

   On that basis alone, the review process should be no slower and probably faster than is currently the case.

   Moreover, by requesting the information in a standardized format, it will be easier to review and, unlike the current state of affairs, available so that if there is a question, the **FDA** auditor will not have to hunt through a

large mass of unstructured records to find the information needed to confirm compliance.

Therefore, the commenters are left with the nebulous objection, "inclusion in the ANDA and NDA and the prescriptive guidelines presented, will ... restrict the development activities of the firm."

Apparently, the commenters choose to ignore the positive benefits of being provided an activities documentation roadmap to providing the Agency with an easily reviewed submission.

Moreover, since this guidance only applies to the information requested, it does not in any way, shape or form "restrict the development activities of the firm," provided that firm's current systems are **CGMP** compliant.

As guidance, it simply outlines what is needed and requests that the needed information be provided in a defined structured manner.

If, *as the commenters assert*, the firm has the information in its files in a format different than that requested by the guidance, the firm may elect to submit it in its original format provided it truly does meet the requests strictures, note the format difference, and provide a simple statement that the alternative format is equivalent to that in the guidance.

"Aegis recommends that sections of this Draft Guidance where the requirements are escalated be eliminated or changed. These sections are detailed below. In addition, Aegis recommends that the 8 pages of the PDR be replaced with a list of topics that the ANDA and NDA applicant should consider in the process development of a drug product."

2. For the reasons outlined in **Reviewer's 1**, this reviewer recommends that the commenters' remarks be rejected.

"Discussion:

Aegis finds this draft guidance an escalation of requirements for the submission of ANDAs and NDAs. This escalation occurs in the Pharmaceutical Development Report (PDR) section and other sections of the draft guidance."

3. For the reasons outlined in **Reviewer's 1**, this reviewer recommends that the commenters' remarks be ignored.

"Presently, the information requested for inclusion in the PDR is reviewed with a FDA investigator during a FDA audit. The information is collected as the process is being developed and it is specific to the SOPS of the developer. This new requirement for inclusion in the ANDA and NDA and the prescriptive guidelines, will burden the Agency and restrict the development activities of the firm."

4. For the reasons outlined in **Reviewer's 1**, this reviewer recommends that the commenters' remarks be ignored.

"The burden to the Agency will be in slowing the review and approval of ANDAs and NDA. The PDR will be a large and concentrated report addressing chemistry, formulation and analytical information. "

5. Based on the commenter's own statements, the Agency already has the burden of reviewing all of the information that this draft guidance is requesting be submitted and, because it is in an unstructured mass of records, the Agency currently has the added burden of ferreting out and piecing together the information needed from disparate records.

   Accepting the commenters' remarks, ***the PDR will reduce the burden on the Agency*** – not increase it.

"The typical review chemist does not have the skills necessary to assess the quality of the development activities. This will lead to slower reviews, additional resources and inconsistent implementation of the guidance."

6. While the typical review chemist may exist, this reviewer, for one, has never met or conversed with that person.

   Moreover, while the **FDA** investigator may have as little as the equivalent of a degree in some area of science, like Geology, the personnel that review applications are persons that typically have degrees and often advanced degrees in the relevant sciences (e.g., chemistry, biology, chemical engineering, physics, pharmacy and the like).

   To be a Chemistry Reviewer, you have to be a bona fide Chemist.

   Moreover, such are more likely in today's FDA to have the skills to assess the quality of the development activities in a firm than some who perform the on-site audits.

   In addition, this reviewer's experience is that, as a group, the Review Chemists (working in the same physical location as their supervisors): **a)** tend to adhere to their checklists better and **b)** are able, by looking at the information provided in the formats requested, to ascertain whether or not the information requested has been provided than an equally qualified investigator at a site can by digging through disparate records.

   As Sam Clark, now an ex-FDA investigator in the area of software validation said, "If I ask and you aren't able to provide the documents requested, I need go no further."

   Thus, by requesting the information provided be furnished in a particular format, even filing clerks and computerized systems can be trained to recognize when requested information is missing – detecting missing records in a submission is not "rocket science."

   For all of the preceding reasons as well as those stated in **Reviewer's 1**, this reviewer finds the commenters' list of woes to the Agency not only unconvincing but also at odds with reality.

"The restriction in the development process at the firm will come from the developer's tendency to satisfy the prescriptive requirements of the PDR and not fully explore the process parameters. This will result in a less comprehensive characterization of the process."

7. The commenters' remarks are inconsistent with the fact that the guidance pushes the developer to not only fully explore the process parameters but also to gather and report the documented evidence that supports the development process' validity.

   Since the guidance addresses areas (such as physical properties and physical property interactions) that the current CMC guidance does not, it is, or should be, obvious that the opposite will happen – a guidance-following applicant will provide proof of a much more comprehensive characterization of the process than is done at present.

   Thus, while warning of Agency slowdown and burden, the commenters are actually transferring the firm's concerns of the impacts on its submission schedule to the Agency.

   Based on the preceding realities, the commenters' remarks should be discounted or, in the least, taken with a large grain of salt.

"Aegis recommends that the 8 pages of the PDR be replaced with a list of topics that the ANDA and NDA applicant should consider in the process development of a drug product."

8. This comment is but an almost exact repeat of a remark made earlier (in the sentence preceding **Reviewer's 2**).

"Additional examples of requirements escalation are listed below:

A. Lines 681 - 970 V. Manufacture (P.3)
This section states that a flow diagram should be included for the manufacturing process. Previously, many, but not all submissions included flow diagrams. To require such a diagram is requiring more information in the application."

9. This reviewer agrees with the commenters' first statement.

   Then, the commenters state that "many, but not all, submissions included flow diagrams" – another statement this reviewer accepts.

   However, based on the commenters' first remark, a "should" is not a "must or a "shall," and, therefore, this draft guidance, contrary to the commenters' third statement, imposes no requirement.

   Moreover, again accepting the commenters' observation concerning today's submissions, many already include flow diagrams.

   Thus, flow diagrams or their equivalent have become a *de facto* CGMP requirement even though they cannot be set forth as a guidance requirement – by definition, *guidance* isn ot and cannot be made to be synonymous with *requirement*.

"a. The flow diagram is discussed in lines 782-796 describes in detail the information that should be included. These include weights, critical process controls, and the equipment used. We believe that this is not necessary information for a flowchart and the information already exists in other sections of the application."

10. This reviewer respectfully disagrees with the commenters' remarks concerning what the requested *flow diagram* should cover and thinks, that to cover all steps that fall under **CGMP**, additional steps should be included.

That information exists has no bearing on whether or not a flow diagram should cover that information.

After all without any information, how can anyone generate a flow diagram?

Aren't all flow diagrams high-level overviews of information?

Based on the preceding realities, this reviewer not only supports the scope of the flow diagram currently requested in the draft guidance but also thinks that it should be expanded to cover all aspects of manufacturing from incoming, through in-process, to release and distribution.

"b. Lines 816-822 discuss the description of the manufacturing process and the difference that exists between requirements for an ANDA and NDA. Both of these applications should have the same reporting requirements for the manufacturing process.

11. First of all guidance does not establish requirements; it simply provides an approach to satisfying requirements that the proposing Agency, the **FDA** in this case, thinks is appropriate.

Second, the lines in question state: "**For NDAs, the description of the manufacturing process can be either a detailed narrative description or a proposed master production record (MPR).[22] However, CDER and CBER prefer that a detailed narrative be provided for an NDA. For ANDAs, the proposed MPR should be submitted. A narrative description should be submitted to supplement a MPR when appropriate, for example, when novel processes or technologies warrant description in greater level of detail. Executed Production Records should be provided in R.I.P.**"

Thus, the text cited addresses differences in the presentation of the information requested and NOT differences in what information is being requested."

Third, all such application CMC sections do have the same reporting requirements as set forth, in general, in the CGMP regulations **21 CFR 210** and **21 CFR 211**, and, in specific, in **21 CFR 314** through **21 CFR 320**.

Based on the preceding, this reviewer thinks that the commenters' remarks should be discounted.

"B. Lines 975 - 1126 VI. Control of Excipients (P.4)"

"a. Lines 1084 - 1087 list the criteria needed to justify proposed excipients specification for non-compendial excipients. The criteria include relevant development data, batch analyses, data from drug product stability studies and information that is presented in other parts of the application. The statement that this justification should be as recommended for a drug substance

(which will be given in a forthcoming guidance) is a substantial escalation of current requirements where, per current practice, it is up to the firm to justify the chosen specifications for non-compendial excipients according to their own SOPS."

12. First of all this reviewer agrees with the commenters' implied objection to references to "a forthcoming guidance" that is not even available in draft for review.

However, that text is in **Lines 1081 – 1083** and even these 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 excipients*, is a drug.

Nothing in the proposed text conflicts with the commenters' remark, "it is up to the firm to justify the chosen specifications for non-compendial excipients according to their own SOPS" provided those "SOPS" are **CGMP** compliant.

Therefore, this reviewer finds that the only objection that the commenters make that is valid is the implied one concerning the referencing of non-existent documents.

"b. Lines 1121 - 1126 for novel excipients indicate that full details of manufacture, characterization, and controls with cross-references to safety data should be provided. The disclosure of a novel excipient's manufacturing process to a drug product developer is rare. This information is most likely to be in the DMF. To require the applicant to include this in application is unreasonable and an escalation of requirements.

13. The commenters remark concerning information in a DMF is a red herring because, as the commenters should know, such contingencies are addressed by the applicant's referencing the applicable portions of the DMF and the DMF holder's providing a letter of authorization for the **FDA** to review that portion of the filed DMF.

Based on the preceding, the request for this needed information is NOT unreasonable though, in some cases, it may add to the body of information requested.

Finally, because the information request is contained in a guidance, it establishes no requirements – only provides an approach to establishing that a firm operates in compliance with **CGMP**.

Therefore, the remarks made by these commenters should be discounted.

"C. Lines 1129 - 1509 VII. Control of Drug Product (P.5)
Items a, b, and c represent an escalation of requirements."

14. Because this text is a guidance document, itc annot and does not attempt to change requirements.

It simply modifies the portion of the requirements addressed in the CMC section of an application for which the Agency is requesting the applicant to include supporting documentation that establishes compliance with **CGMP**.

"a. Lines 1153 - 1155 requires that certain in-process tests be performed in lieu of finished product tests (such as hardness and tablet weight) and should be included on the COA. This not a standard practice and it does not appear in the GMP regulations. This is not consistent with current requirements and should be changed."

15. As the following will show, the commenters' remarks totally misconstrue the text and the factual realities associated with the text.

In context (**Lines 1144 – 1162**), the text in question states:

"The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- **tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))**
- **all analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30]**
- **acceptance criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC)**
- **release and shelf-life acceptance criteria when both are used."**

The first bullet contains the text from the cited lines (**Lines 1153 – 1155**).

All that is requested here is for the applicant to identify which tests on the requested global specifications' sheet's listing of tests that **that can be performed in-process in lieu of testing the finished product"** with the parenthetical request that **"the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))."**

Again the text makes requests – it does not establish requirements.

Moreover, the text does not request, "certain in-process tests be performed in lieu of finished product tests."

However, factually, the test "tablet weight" is required by the **CGMP** regulations (**21 CFR 211.110(a)** and **21 CFR 211.110(b)** on each in-process batch test where such test is appropriate.

The cited passages state (emphasis added):

"(a) **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. Such control procedures shall include, but are not limited to, the following, where appropriate:**

(1)Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions.

(b) **Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.**

Based on the preceding, tablet weight (for variation) is a test that is explicitly required for tablets because the clause "where appropriate" is required to be taken to mean "unless the test is inappropriate for the drug product in question i.e., for example tablet weight variation for an ointment product in tubes.

Moreover, when tablet hardness variation is linked to variation in the release of the active or actives from a tablet drug product, then hardness monitoring is also required.

Thus, contrary to the commenters' remarks, such in-process testing is required by the **CGMP** regulations on batch representative samples (**21 CFR 211.160(b)(2)**).

While requesting such to be reported on the batch analysis report (e.g., COA) may differ from the practices of these commenters' firm, the tests themselves most certainly are "consistent with current requirements."

Based on all of the preceding, the text simply only requests that **CGMP**-required testing be reported on the batch analysis report when that testing is done **"in lieu of testing the finished product."**

Therefore, the request is reasonable and valid and the draft text should retain it in the final guidance.

"b. Lines 1286 - 1305 require that batch analysis be provided for ALL batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies. To include ALL batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies will involve a huge amount of data of the type described in lines 1297 - 1305. This requirement should be changed to pivotal studies only."

16. This reviewer disagrees with the commenters' remarks because the Agency needs that information to determine whether or not the firm's conclusions and interpretations of the studies submitted are valid and predict that the firm's manufacturing, processing, packing, packaging, labeling, testing and quality control operations are **CGMP**-compliant.

Applications that lack any of the requested information may be rejected or placed on hold – thus delaying the application's approval.

Thus, it would seem that firms would be anxious to provide all of the data requested and more to ensure that an overlooked study will not hold up their application's review.

"c. Lines 1330 - 1334 presentation of assay, impurity results, degradation products and residual solvents results from ALL batches will involve a huge amount of data. This requirement should be changed to include pivotal batches only."

17. **See Reviewers' 16.**

Moreover, as written, the commenters' remarks only apply to NDA applications because these do have a batch or batches of the drug product that are used in the pivotal (or key) clinical trials that can be properly identified as a "pivotal batch" or "pivotal batches."

In an ANDA application, the key batch is called the bioequivalence batch.

In such applications, the term pivotal is <u>not</u> used nor would it be appropriate to do so.

"These examples of requirements escalation are the strongest cases where the draft guidance has increased the requirements as compared with the current guidance and practice. The above references illustrate how and where escalations of requirements occur and should serve as examples to change the draft guidance to better reflect current requirements.

<u>Recommendations</u>:

Aegis Pharmaceuticals recommends that the 8 pages of the PDR be replaced with a list of topics that the ANDA and NDA applicant should consider in the process development of a drug product.

We also recommend that the examples of escalation of requirements listed above be changed to reflect current approved guidance and practice. In addition, the draft guidance should be reviewed for additional examples of escalating requirements and they should also be revised to reflect current approved guidance and practice."

"Aegis believes that following the recommendations made in our comments will reduce and potentially eliminate the increasing requirements reflected in the draft guidance."

18. For all of the reasons previously stated by this reviewer, this reviewer recommends that these commenters' remarks be discounted.

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

Harry L. Welles' Submission Dated June 4, 2003
To Docket 02D-0526: "C-02"

Note: The original INTRODUCTORY 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. In this review, this reviewer's comments are made after the commenter's remarks and, when the commenter's remarks are "boxed," are placed inside the box.

This commenter begins by stating,"

Thank you for the opportunity to comment on the draft Guidance for Industry, *Drug Product, Chemistry, Manufacturing, and Controls Information*. This is an extensive document that clearly represents a considerable investment of FDA resources and contains some important considerations for presenting the drug product section of an application.

Although comments on draft guidances often focus on the parts of the guidance that the commenter would like to have changed, I would like to highlight a few important points in the guidance that that I believe are very helpful and which should be retained in the final guidance. These are the following:"

Line Number	Comment
1457, 1480	The concepts of sunset test protocols and interim acceptance criteria are very useful. Having them in the guidance may eliminate some barriers to their implementation. In some instances, the use of sunset test protocols could streamline the regulatory processes for both FDA and industry while ensuring the delivery of quality drug products to the marketplace. In general, this reviewer agrees with the commenter provided full **CGMP** compliance is established and maintained. Similarly, this reviewer is a strong proponent of *scientifically sound* and *appropriate* predefined contingent (hierarchical) sampling and testing plans in applications.
885-901	The discussion of reprocessing is clear, concise, and provides a very reasonable approach. While this reviewer agrees, this reviewer also thinks that the "Glossary" should define this term and, firms electing to include such in their applications should provide detailed explanation (justification) of the reasons that their process could not be developed to be robust enough that such is not required.
1793	The concept of providing EPRs for representative batches is good and should be retained. The provision of EPRs for all stability and BA/BE lots, adds bulk and complexity to the application, but may not always serve a useful purpose. This reviewer agrees with the commenter's first statement, but takes exception to his second because all such data serve to increase, or decrease, as the case may be, the Agency's understanding as to whether or not the application presents a **CGMP**-compliant picture of the processes, controls and systems that will ensure the safety, efficacy and quality of each RELEASED unit in each ACCEPTED batch should be safe, efficacious, and, if tested, meet the drug product's established post-release specifications for that unit.

"I have several general comments:

1. For consistency with ICH, replace "CMC" with "Quality" wherever possible."

In general, this reviewer agrees that, for harmonization with the ICH, "CMC" could be replaced with "Quality" wherever possible, but, upon reflection and in consideration of the importance of names, would recommend that it be replaced with the phrase "CGMP Quality" so that it is harmonized both with the ICH and the **FDC Act**'s requirement for **CGMP** that the CMC section's documentation is supposed to demonstrate.

"2. The use of the outline numbering for the CTD headings (with CTD numbers in parenthesis) is cumbersome. If FDA needs to maintain the outline numbering system for the guidance, perhaps it could be used for Sections I and II of the guidance, then the rest of the guidance could be presented in the CTD format."

While this reviewer agrees with the commenter's observation that the outline (and referencing) system used in this guidance is cumbersome, this reviewer would, as others have, suggest that the outline simply use the CTD referencing system.

"3. There are several places where this guidance calls for information that is more properly a GMP requirement. These include provision of duplicate test results (supplier and applicant) for components; in-process stability results; and stipulation of different requirements, depending on whether the applicant or the supplier performs full testing. These should continue to be GMP requirements and not be added to the application. This information should be reviewed during an inspection, rather than in a registration document.

This reviewer rejects this commenter's recommendation on several grounds:

A. Nothing in the statute (**21 U.S.C. Title 9, Federal Food, Drug, and Cosmetic Act**, as amended [commonly abbreviated as "**FDC Act**"]), the **CGMP** regulations governing drug products (**21 CFR 210** and **21 CFR 211**), or the filing requirements for ANDAs and NDAs (**21 CFR 314** and following) that this reviewerc an find prohibits the **U.S. Food and Drug Administration** ("**FDA**") from requesting the submission, *in an application*, of any document that an applicant is REQUIRED: **a)** to have generated and maintained to comply with the statute or with **21 CFR 210** or **21 CFR 211** and **b)** by statute or regulation to be available for inspection.
B. The responsibility for establishing that processes, controls and drug products comply with **CGMP** is not borne solely by the **FDA**'s inspectorate – all **FDA** personnel directly or indirectly involved in the review of an application have a duty to ensure that what is approved does comply with **CGMP** as it is defined in **21 U.S.C. 351(a)(2)(B)** and reiterated in **21 CFR 210.1(a)**.
C. The Agency therefore has the discretion of requesting any such document that is required to exist be submitted to the Agency or having its personnel inspect that document in an on-site audit.

D. The providing of the information requested in the formats requested will not only reduce the review burden upon the inspectorate (a dwindling resource in the Agency) but also speed the review process by: **a)** ensuring that the requisite **CGMP** compliance is supported in the documentation submitted (eliminating review holds when a PAI inspection finds major deficiencies that would have been obvious had the Agency requested the information in the submission) and **b)** providing the inspectorate (committed to using a systems approach to inspection) with a clearer picture of which systems need the more focus. [In essence, the additional information constitutes an in-depth pre-audit survey of the sponsor's sites and systems. In addition, by asking the information be provided in a structured format that facilitates review, the Agency will save those person-days that the inspectorate has been spending assembling and collating that same information – thus allowing the Agency to increase its review efficiency by minimizing the clerical burden on the inspectorate.]

Based on the preceding factual realities, the commenter's remarks should be ignored.

"Specific suggestions for revisions are in the attached table.

If you have questions, or if I can be of assistance in any way, please feel free to contact me at 513-831-5802 or hlwreg@fitse.net."

Line Number	Proposed Revision	Rationale
65-74	Eliminate the reference to drug substance requirements. This reviewer disagrees with this comment.	This is a drug product guidance. Drug substance requirements should be addressed in the drug substance guidance. In the context presented (an introduction to the CTD), the comments made pertaining to the drug substance are appropriate and some cannot be deleted without misrepresenting what the Module 3 is supposed to address.
320-322	Delete the sentence "Components that are used in the manufacture of the drug product and do not appear in the finished drug product ... should be identified as processing aids.". This reviewer does not agree.	This is very prescriptive. At times it may be useful to provide other information about these components. How is it that suggesting that such "**should be identified as processing aids**" prohibits the applicant from providing other information about these components? Since the guidance simply suggests a "name" for such components, nothing other than the applicant's decision prevents the application from providing other information about these compounds. In fact, the guidance suggests that a specification should be provided for each such processing aid (**Lines 1008 – 1010**).

Line Number	Proposed Revision	Rationale
362-680	Delete the pharmaceutical development section in the FDA guideline and refer to ICH. This reviewer disagrees.	This section in the FDA guideline is very detailed and prescriptive. My understanding is that there may be an initiative in ICH to develop a harmonized guideline on pharmaceutical development. FDA should not preempt that effort. If ICH does not develop a harmonized guideline, the CTD guidance serves as an adequate starting point for this section and the applicant should have some flexibility in presenting the data. The **FDA** is charged with assisting the industry to operate in compliance the requirements of the **FDA Act** and **CGMP**. What the ICH may, or may not, do in the future is not certain. Given the requirements of **CGMP**, the CTD guidance does NOT serve "as an adequate starting point for this section." Because the document is guidance and not requirement, it does not, as the commenter implies (by using the terms detailed and prescriptive) restrict the flexibility of the applicant. Provided the applicant's alternative "prescription" is equivalent to the **FDA**'s guidance, the applicant should have no problem with it. Thus, though detailed, the guidance offered is rational, needed, and should be retained – ICH can then use it as the basis for their initiative when and if they decide to undertake such.
549	Replace "study numbers" with "appropriate cross reference identifiers". Agreed.	As written, this implies that there will be stability "reports" with title pages, etc. in the Quality section, such as is done for the Clinical section. This is not necessarily the case. More general wording should be used to allow for differences in approach.
710-712	Delete this section. This reviewer disagrees.	Personnel information is provided in the drug establishment information attachment to Form 356H. This form is updated and submitted with every registration filed. It should not be necessary to repeat this information within the body of the Quality module. Duplication in the quality section is redundant and the information there become get outdated. The commenter ignores the facts: **a)** upon submission the reviewer is supposed to be ready for inspection, **b)** the applicant is already required to keep the referenced information up to date, **c)**, since the inspectorate gets a copy of the CMC "Quality" module, providing this would expedite the review process, and **d)** the Agency has no leverage to ensure that the component suppliers keep that information up to date. Based on the preceding facts, the Agency has properly included a request for this information.

Line Number	Proposed Revision	Rationale
784-785	Delete "(e.g. weighing of components through finished product release)". This reviewer respectfully a) disagrees with the commenter's remarks about what the requested flow diagram should cover and b) knows, that to cover all steps that fall under **CGMP**, additional steps should be included.	Requiring basic plant operations such as weighing and release to be shown in the flow diagram adds to the complexity of the diagram without providing useful information. The flow diagram should focus on the major manufacturing unit operations. Discounting the initial sentence as a mixture of unsubstantiated claims and irrelevant facts, this reviewer agrees with the commenter – "the flow diagram should focus on the manufacturing unit operations." However, regardless of the complexity, or the lack thereof, the routine manufacturing unit operations addressed by **CGMP** start with: a) receipt of components; b) sampling of components; c) testing of components; d) release of components to production; e) allocation of components for a given batch; f) start of production of a batch; g) charging of components for the first phase of manufacture; h) in-process control of the first phase of manufacture; i) – k) sampling, testing and/or examination, and release of the output of the first phase in the manufacture of a batch to the next phase; and ends with unit operations: ia) – ic) the inspection (sampling and testing and/or examination), and release of the finished packaged batch of drug product; and id) the transferof the released batch from manufacturing to warehousing or distribution. Therefore, the requested diagram (which may be composed of a series of "sub" diagrams) should address all regulated manufacturing unit operations. Since that is the case, the preceding should be included in said diagram or set of "sub" diagrams.
824-830	Move the paragraph on ruminant-derived materials to the regional information. Provided the move is to the appropriate Appendix in Module 3, this reviewer concurs.	This is a US-specific requirement and not part of the manufacturing process description. To have the requested statement here introduces US-specific information into a document that otherwise would be suitable for use in most geographic regions. Regional requirements should be addressed in Module 1 or the Appendices to Module 3. Though not bound by the ICH guidance, the draft "CGMP Quality" guidance's format should parallel that of the ICH to the extent that it legally can.
855-865	Delete "as illustrated in the following examples:" and the bulleted list. This reviewer disagrees.	The general statement that a control "may or may not be critical" is sufficient. The applicant should not have any trouble in interpreting that. If FDA thinks more detail is necessary, a discussion of the principle involved in deciding if a process is critical would be a better approach. This reviewer recognizes the power of providing examples as an aid to the understanding of what is being requested. Further, this reviewer knows that those who fill out any information request appreciate examples and bulleted list that they can use as "check lists" to ensure all applicable requests are satisfied.

Line Number	Proposed Revision	Rationale
927-929	Add a statement such as "Although they are considered product critical process controls; some tests on intermediate may not need extensive justification if they are consistent with current industry practice or compendial standards, for example, hardness or assay of a core tablet prior to coating.". This reviewer disagrees.	FDA has defined tests done on intermediate products as critical process controls, however, the acceptance criteria for some of these are well established and need no further for justification. The commenter's statement is false. Factually, the **CGMP** regulations define the types of control and procedures (tests) to be considered for use on each batch and specifies, "**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.**" Thus, whenever a firm finds that any of these are required to control each batch they become critical controls. If they are not such, then they should either not be being used by the firm or their use should be justified in as PQIT. In addition, the **CGMP** regulations require each manufacturer to establish (justify that) that the controls they use are ***scientifically sound*** and ***appropriate*** **(21 CFR 211.160(b))**. As the Agency knows, factually it has been established that the requisite controls are not those in the **USP** or **NF** because these are ONLY *scientifically sound* and *appropriate* for drug-product in commerce – not *necessarily* for in-process materials. In addition it has been established that the sample numbers and/or used in many cases by the industry, including most published examples, do not, as Agency management is aware, meet the requirements of **21 CFR 211.160(b)(2)** and/or are, for other reasons, not ***scientifically sound***. Based on the preceding it is, or should be, obvious that: **a)** *This added text should be rejected* and b) **b)** *Each submission should provide a* ***regulation-compliant***, ***scientifically sound***, *and* ***appropriate*** *justification* for any in-process control that is required to be used on each batch (to ensure compliance with **21 CFR 211.110**). Factually, most firms do not perform tests or examinations when they know that these tests or evaluations contribute nothing to the their requirements for product quality mandated by the government or, for appearance, by the consuming public. If tomorrow the consumer were to magically stop equating physical appearance and appearance uniformity in a coated tablet to the drug-product's quality, then the manufacturers would drop those attributes from its current statistical attributes inspection plans the very next day.

Line Number	Proposed Revision	Rationale
982-983	Delete "and the applicant intends to perform full testing on each batch received,". This reviewer opposes this deletion.	Full or reduced testing by the applicant is a GMP issue, not a registration issue. First, by taking the phrase out of context and making a tangential issue into the "rationale" for the proposed change, the commenter deliberately distorts what is being said. The text in question (**Lines 981 – 987**) states (underlining added): "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." **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 any additional information.** Deleting the second condition would subvert the intent of this text – to insure that the FDA 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 perform. Thus, though wrapped in the language that would lead one to believe that this is an issue between a CGMP requirement and a registration requirement, this commenter is attempting to have the text modified to escape having to report exactly what testing the supplier and the applicant are doing. Moreover, the commenter's rationale has no basis in fact. Nowhere in the **CGMP** regulations or the **FDC Act** does this reviewer find any prohibition for the Agency's request for an applicant to provide the requested documentation in support of an application and require it to be only reviewed as part of an inspection. Contrary to the implication of the commenter's remarks, all **FDA** personnel are charged with ensuring that all manufacturing practices and drug products comply with **CGMP**. Thus, this is a registration issue because the reviewer is required to ascertain **CGMP** adherence prior to recommending approval. Second, guidance is guidance – not requirement. Third, the documentation requests are justified because they provide the supporting evidence (proof) that the applicant's assertions are valid and/or **CGMP** compliant. Finally, the phrase is a critical conditional limit on when the applicant may simply list the compendial monograph without explanation or justification. For the preceding reasons this commenter's suggestion should be rejected.

Line Number	Proposed Revision	Rationale
982	Replace "with no additional testing" with "and no additional testing is needed to ensure the suitability of the excipient in the product". This reviewer must and does oppose this change.	Additional testing is done from time-to-time for a variety of reasons. This section should focus on attributes of the excipient that ensure product quality. Having proposed removed half of what the commenter must really feel is an onerous request, the commenter turns his attention to "adjusting" the first restrictive clause to his liking. Again, by taking the phrase out of context, dividing the changes suggested for the same text passage, and making a tangential issue (what "This section should focus on") into the "rationale" for the proposed change, the commenter again deliberately distorts what is being said. The text in question (**Lines 981 – 987**) still states (underlining added): "Compendial-Non-novel Excipients: When a compendial excipient is tested according to the monograph standard <u>with no additional testing</u> 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." **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 any additional information.** However, were this change and the previous change to both be made, the text would be reduced to: "Compendial-Non-novel Excipients: When a compendial excipient is tested according to the monograph standard ~~with no additional testing~~ and no additional testing is needed to ensure the suitability of the excipient in the product ~~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." As proposed, the applicant could simply list the excipient *whenever any one monograph standard test* is performed because this commenter did not insert the word "full" before the word "monograph" and all compendial-non-novel excipients would simply be listed This is the case, because the applicants would continue doing what most are doing now, they ignore the strictures of **21 CFR 211.84(d)(2)** that <u>require</u> doing ***at least one specific identity test*** before the supplier's report of analysis can be used in lieu of testing. Instead they claim to follow **21 CFR 211.84(d)(1)** that only requires an identity test, but instead of an ***identity test***, they perform an "Identification" test. Then, the use the results of that "Identification" test to justify accepting the supplier's report of analysis. Finally, based on doing periodic cross checks of the supplier's results with theirs on some lot, they falsely claim that they are operating in compliance with **CGMP**. Hopefully, the Agency, reading this reviewer's comments, will crack down on this violative practice that, as this reviewer has pointed out, seems to be widely used.

Line Number	Proposed Revision	Rationale
989-990	Delete "The P. 1.4 to P.4.4 for each individual excipient should be grouped together in the application.". This reviewer disagrees with the commenter's proposal.	This organizational detail has some merit, but it is inconsistent with the organization of the CTD guideline and granularity document. If FDA disagrees with the organization of CTD it should work through ICH to change it. As the Agency of a sovereign government, the **United States of America**, the **FDA** is, in no way, constrained by the guidance issued by the ICH, a non-sovereign body ("NGO.") Whenever the **FDA** chooses it may ignore such guidance and should in this case because grouping the data by excipient makes it easier for the application reviewer to understand whether or not the specifications for a given excipient are adequate for the use of that excipient in that formulation. Frankly, this reviewer thought the industry was all for doing what it could to expedite the review process but time and time again comments such as this remind this reviewer that the industry's agenda seems to be other than the one they espouse in public. Therefore, this reviewer again recommends that the Agency leave the draft language as it is and ignore this commenter's proposal.

Line Number	Proposed Revision	Rationale
1022-1030	Delete this paragraph. This reviewer not only disagrees but also proposes that this paragraph be corrected to fully mesh with all of the applicable CGMP requirements for all components as shown on the following page.	1. Full testing must be done by either the manufacturer of the excipient or the applicant. However, the issue of whether the applicant does full testing or reduced testing is a GMP issue and should not be part of the application. 2. The statement regarding specifications and testing for polyols is important; however it should be addressed independently of the drug product guideline. Before considering the commenter's avowed rationale, the text needs to presented so that anyone reading either the comments or this reviewer's appraisal thereof can know what was stated. The text in question states: "In addition to listing all the tests for an excipient, the specification should 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).[27] At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1)). However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities, and the specification should include testing for potential impurities and contaminants for each batch received by the drug product manufacturer. [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 tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices." Thus, the first thing this reviewer noticed is that this paragraph has nothing to do with "full testing" but rather with 1. The identification of who (supplier or manufacturer will do each test), and 2. The need for safety related tests when there is an inherent "concern" (such as: potential toxic impurities, microbial or BSE contamination, product mixing and mix-up in an integrated facility) associated with a given excipient. Based on what the paragraph says, it is obvious that this text needs to be retained. It is equally obvious that this commenter's rationale seems to have been crafted to imply that the paragraph dealt with issues other than those that it does. For all of these reasons, this commenter's remarks should be ignored. Moreover, as written, the text misstates the **CGMP** requirements for the acceptance of the supplier's report of analysis (COA) in lieu of full compendial testing and, where required, tests for other concerns and properties. To correct that misstatement, this reviewers again offers the alternative test that is presented on the next page

Line Number	Recommendation	Revision (Its rationale is on the previous page)
1022-1030 (cont.)	Change the text as shown in adjacent column so that it fully meshes with all of the CGMP requirements for component acceptance.	In addition to listing all the tests for an excipient, the specification should 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).[27] At a minimum, the drug product manufacturer must perform **at least one specific identify test (21 CFR 2 11.84(d)(2)) on a lot-representative set of samples from each shipment of each lot[27a] when the manufacturer elects to use information from the supplier's COA in lieu of full testing.** However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities, and the specification should include testing for potential impurities and contaminants for each batch received by the drug product manufacturer. [27] **To elect to use this option,** the drug product manufacturer must: a) perform at least one specific identity test on lot-shipment representative samples from each lot and b) 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 tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices." [27a] **The drug manufacturer must comply with the requirements for component sampling set forth in 21 CFR 211.84(b),** "Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by Sec. 211.170" and 21 CFR 211.160(b)(1), "Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration." [**Note:** When the full monograph option is chosen for excipient testing, there is no need to cite **21 CFR 211.84(d)(1)** and when the **21 CFR 211.84(d)(2)** option is elected, citing **21 CFR 211.84(d)(1)** would be incorrect. Therefore, the guidance should refrain from citing **21 CFR 211.84(d) (1).** Thus, the Agency should cite **21 CFR 211.84(d)** when addressing full monograph testing and **21 CFR 211.84(d)(2)** when addressing either aspect of the **"Accept COA"** option: a. ***At least one specific identity test*** or b. ***Establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.***]

Line Number	Proposed Revision	Rationale
1089-1094	Delete this paragraph. This reviewer disagrees and recommends that the draft text be retained "as is.".	Comparison of COAs from the manufacturer and the applicant is a GMP issue. Requiring such a comparison in an application is an unjustified new regulatory requirement. Before proceeding to review the proposal, the text needs to be considered. The text reference states: "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). Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged." The first thing this reviewer sees is that no comparison of COAs is being requested, all that is being requested is a copy of the supplier's COA and the manufacturer's results for the same batch. Moreover, the request is that the information be provided for the materials used to in the EPR batches. *Since no comparison is requested much less required,* this rationale is specious on its face and need not be addressed further. Based on the preceding, this text should be retained and incorporated into the final "CGMP Quality" guidance.

Line Number	Proposed Revision	Rationale
1153-1155	Reword to say "if a test that is usually performed on the finished product, is instead performed in-process, the in-process results should be provided in the batch analysis. This reviewer objects for the reasons stated and knows that this text should be retained and incorporated into the final guidance.	Clarity. In context (**Lines 1144 – 1162**), the text in question states (with pertinent text underlined): "The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify: • tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis)) • all analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30] • acceptance criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC) • release and shelf-life acceptance criteria when both are used." The first problem that this reviewer has is the one of grammar – "the specification sheet should also identify" "if a test that is usually performed on the finished product, is instead performed in-process, the in-process results should be provided in the batch analysis." How can a specification sheet identify a future condition in a given case? Obviously, it cannot. Since the commenter stated that the rationale used was clarity, it is also equally obvious that he failed to add any clarity with the his substitution Based on the preceding alone, the present text should be retained unless other better text that preserves the request. Moreover, this commenter again attempts to turn a simple request "tell me which in-process tests, if any, can be used in lieu of testing the drug product" into something else apparently because, given his suggested alternative, this commenter is seeking to conceal the exact nature of the applicant's in-process and release testing programs.

Line Number	Proposed Revision	Rationale
1174	Delete the reference to in-house method numbers in the table. This reviewer disagrees with this comment and would suggest that the example table be modified to contain a footnote that states, "When the firm does not use any formal system of method identification, other than the name of the method, that full name should be included in the table.	In-house numbers are not necessary for method identification. Alternative naming conventions could be used, for example Reverse Phase HPLC Determination of Compound X. With electronic cross-references, this is clear and concise. First of all, while technically true, the commenter's first remark is disingenuous because the reality is most all firms use formal identification systems to name, track and control their methods. In almost all cases, that identifier is considerably shorter than the full name of the method and is, therefore, more suited for inclusion in a physical tabular format. Moreover, even if the applicant submits an electronic submission, where physical width is not a concern, the primary electronic links in that submission are the method identifiers. When reviewing an application, it facilitates the review when the primary and alternative method or methods, if any appear next to one another. Second, contrary to common sense, this reviewer states "With electronic cross references, this is clear and concise" – a sentence that begs anyone to know for certain what is clear and concise and to what, if not an identifier, do the cross reference refer? Based on the preceding, this reviewer accepts that, to allow for the possibility that some firm somewhere only uses method names, a naming alternative should be considered.
1288	Reword to say "Batch analysis data should be provided for batches used in relevant clinical efficacy and ..." This reviewer objects to this change and would propose the following as a ***scientifically sound*** and ***appropriate***, CGMP-compliant alternative for **Lines 1288 – 1291**: **"Batch analysis data should be provided for all batches used in studies designed to assess clinical efficacy and safety, bioavailability, bioequivalence, and primary stability."**	All studies and/or batches may not be relevant to the application, for example exploratory studies for other indications. As an investigator having in-depth experience in investigating production process for the root causes of the differences between batches and the factors that affect or correlate with drug-product batch values, the requested information is crucial to determining whether or not a process and the controls on it are a) operating in compliance with CGMP and b) capable of producing batches of drug product that are sufficiently defined and controlled to the point that the data obtained predict that all of the units in the batch would, if tested, pass. In addition, as written, this reviewer's change partially addresses the commenter's concern ("studies and/or batches may not be relevant to the application, for example exploratory studies for other indications") because the data from all such studies is relevant to assessing the performance of the applicant's systems. . Further, by making the change in the manner proposed by the reviewer, this reviewer avoids introducing the obvious ambiguity that inserting the word **"relevant"** would create – because what is relevant depends upon the "person" making the "relevance assessment" while the designed purpose of each study is supposed to be clearly defined before the study is initiated.

Line Number	Proposed Revision	Rationale
1286-1334	Eliminate the requirement for CofAs for all batches. This reviewer opposes the changes proposed by the commenter and, for the reasons stated, believes that the draft text, **"The batch analysis reports (e.g., COAs) and collated batch analyses data should include a description of the batches,"** should be incorporated "as is" into the final guidance.	This section calls for CofAs for all batches & collated batch analysis data for some tests. Providing tabulated batch analysis data on all relevant batches would be a clearer and more practical way to present the data. The use CofAs is not a clear or efficient way to present data on multiple clinical, safety, BABE, and stability lots and they do not add anything useful to the application. Documentation should be checked during inspections, not as part of the review of the application. After stating what is requested, this commenter begins by making an unsubstantiated claim, "Providing tabulated batch analysis data on all relevant batches would be a clearer and more practical way to present the data." The commenter continues with more unsubstantiated claims, "The use CofAs is not a clear or efficient way to present data on multiple clinical, safety, BABE, and stability lots and they do not add anything useful to the application." Then, the commenter again plays another verse of his favorite tune, "Documentation should be checked during inspections, not as part of the review of the application." This reviewer disagrees with the commenter's broad generalization concerning COAs, "tabulation" (collation) of data, and review efficiency. Second, which is needed, batch analysis records or data collations, depends upon what the reviewer's concerns are and, since the Agency that has the relevant review experience and is making this request, this reviewer must defer to their judgment of what is needed for the efficient review of an application. Third, the batch analysis reports, when structured as the Agency requests, do provide significant relevant information beyond the data. Further, the commenter's last remark is a conundrum, since PAI inspections are integral parts of application review, what does, "Documentation should be checked during inspections, not as part of the review of the application" really mean? Factually, by requesting that pertinent documentation be submitted with the application, the Agency is: **a)** ensuring that the data they need to properly review an application has been requested and hopefully provided and **b)** conducting an effective pre-audit survey of the components, systems, controls, and the drug product that are to be audited during the PAI inspection. In the first instance, conforming applications should generate many fewer "data" holds than at present. In the second, the **FDA** inspectorate will be much better able to generate targeted site-specific audit plans and, *relieved of much of the burden of doing what is being requested of the submitter* (collating the information from different batches, for example) should be able to perform more inspections focused PAI inspections of shorter duration. In sum adherence to the proposed guidance will shorten the review period *vis-à-vis* submitting a current application.

Line Number	Proposed Revision	Rationale
1343-1346	Revise to say "Potential drug-product impurities should be listed. These should include degradation products active ingredient, and residual solvents. For some combinations of drug, dosage form, and route of administration, enantiomeric impurities, excipient degradants, and/or leachables from the container closure system may also need to be considered. For the reasons stated, this reviewer opposes the commenter's proposed changes.	Not all of the listed sources of impurities are relevant in all of the cases. In general it serves little purpose to discuss well known excipient degradation products for a solid oral dosage form. Notification that the applicant should consider other sources of impurities in specific instances should be sufficient. First, this reviewer agrees with the commenter, "Not all of the listed sources of impurities are relevant in all cases." Thus, he was perplexed to see that the commenter proposed to change the word "expected" to "potential" even if the scope of the request were restricted to the drug product. The commenter's second remark is a generalization that adds little to support the change proposed. In the third statement, the commenter's remark seems to go against the industry's position that applications be treated uniformly because it suggests that each reviewer or review team should decide the scope – an approach certain to lead to variable levels of concern. Moreover, the proposed changes would also, if adopted, lead to ambiguity and variable review outcomes for, in the case of ANDAs, submissions for the same drug products submitted in different years. The Agency's request seems much more likely to result in improving application uniformity, application review uniformity, and facilitated application review than the commenter's alternatives.
1346-1347	Change to read "Drug substance process impurities that carry over into the drug product should be identified here, but need not be discussed further unless they are also degradants." This reviewer proposes that a simpler alternative wording considered, "**For example, drug substance process impurities that could carry over to the drug product should be listed here**" since, upon reflection, this reviewer sees no need for the modifying clause, "**even if ...**"	Discussion in the drug substance section is sufficient. Before commenting, the text needs to be viewed. The text in question (**Lines 1346 –1349**) states: "**For example, drug substance processi mpurities that could carry over to the drug product should be listed here even if they are normally controlled during drug substance testing and will not be included in the drug product specification.**" At first glance, there seems to be little difference between the effect of the two texts because "**listed here**" and "identified here" are effectively the same thing. However, the difference between "carry over into" and "could carry over into" is significant. In addition, the difference between the locally applicable modifier, "even if they are normally..." and the more globally reaching modifier "but need not be discussed further unless..." is also significant. Based on the preceding, this reviewer will defer to the **FDA** with respect to the change of modifier clause but recommend that the word "could" be retained and the modifying clause be removed as superfluous.

Line Number	Proposed Revision	Rationale
1570-1571	Delete "Stability study reports should also be included.". This reviewer disagrees; Each CGMP-compliant stability test generates a report. The guidance text in question should be kept as it is.	This assumes that freestanding stability reports are written. The guidance should describe the information needed in the application, and allow flexibility in the format. The cited statement does not, as the commenter states assume that any particular type of stability report is written. It simply presumes **CGMP** compliance. **21 CFR 211.194(a)** outlines all of the items that a lab record must contain. **Sec. 211,194(6)** requires: "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." **21 CFR 211.194(e)** requires: "Complete records shall be maintained of all stability testing performed in accordance with Sec. 211.166. Thus, all stability records contain a report, "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." Thus al stability studies generate reports and the commenter's remarks are, at best, unaware what CGMP requires vis-à-vis stability testing.
1573-1593	Move the section on analytical procedures to line 1623, after the section on stress studies (1622). This reviewer agrees.	Information on analytical procedures may apply to all three types of studies (formal, supporting, and stress studies). A stand-alone section on analytical procedures would be a more straightforward way of presenting it, rather than including it in the formal studies.
1580	Delete "(e.g. weight loss)". For the reasons stated, this reviewer does not agree with simply omitting the example. [**Note:** this reviewer would suggest that, in the future, the Agency could choose a different test as its example to nip such in the bud – this reviewer would suggest *"closure opening torque"* because most don't even presume to know how to do the test much less how to do it properly and, in many cases, the test is critical to ensuring lifetime closure integrity, especially for drugs packaged in unit-of-use containers.].	In most instances determination of weight change of a product with a calibrated balance is a standard laboratory procedure and should not require presentation of the procedure and validation data. Factually, based on experience in more than a dozen US and foreign laboratories, there is no one standardized procedure that all laboratories use nor, for that matter, a uniform calibration procedure for the balances used or uniform balances types. As a Ph.D. Analytical Chemist and former Quality Control director overseeing the operation of the internal RM, Validation, In-process, Release, Stability, Complaint and method's improvement and validation lab functions as well as several specialized contract labs, having worked with the lab operations in more than a dozen other firmsin the United States, United Kingdom, Japan, Germany, France and China, this reviewer can attest to the need for labs to have and the Agency to request proof of the reliability of even the simplest unit operations.

Line Number	Proposed Revision	Rationale
1607-1613	Delete the words starting with "Stability data to support holding ... " to the end of the paragraph. This reviewer strongly opposes this deletion for all of the reasons stated – the draft text, or, if such exists, an improved version thereof should be incorporated into this final CMC guidance. [**Note:** Lacking the data requested, an application reviewer cannot ***know*** that the holding times proposed in an application are scientifically sound and appropriate – a **CGMP** requirement. *If these holding times are not substantiated by the data provided,* then, the prudent application reviewer could place the application on hold and request the applicant provide said data. *Most firms claim they do not want to delay their applications.* If this is the case, *prudent firms will report the stability data that support any and all hold times not just those longer than 30 days.* Finally, *because this document is guidance,* a firm may choose to follow the course that this commenter has proposed instead of the one the Agency has proposed.]	In-house holding of in-process materials should be considered a GMP requirement, not part of the application. In addition, these are not "supporting studies" as defined by ICH Q1A. Contrary to the position stated by the commenter in his first statement, in addition to the drug product ("finished dosage form"), the Agency is charged with evaluating whether or not the production processes and controls do, or do not, comply with **CGMP**. Apparently the commenter has overlooked the specific requirements that address the issue the commenter raises. The applicable section is **Sec. 211.111 Time limitations on production** states (emphasis added): "**When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.**" Thus, while the applicant is required to establish time limits for the completion of each phase whether that limit is one day, one week, one month or longer. The Agency recognizing the burden that supplying all of the required studies would impose has judiciously limited their request to a hold period of 30 days or longer." Thus, the request is very reasonable. Moreover, were it to be removed, each application would be subject to the judgment of the application reviewers as to what the "*time-delay start point*" should be for requesting such studies – *silly me, thought the industry was for uniform reviews.* As to the commenter's second remark, concerning ICH Q1A, the following realities apply: 1. No guidance is perfect. 2. The ICH guidance is not binding upon the FDA 3. Recognizing this deficiency hopefully the ICH will adjust their understanding of supporting studies to include those required to support in-process hold times. Of course, firms can avoid having to submit this information simply by holding all of their in-process materials for less than 30 days (as measured from the date and time of completion of the preceding step to the date and completion of the next step). Of course, they will still need to do the studies on to beyond the maximum times projected between steps and have those studies ready for the PAI reviewer to inspect.

Line Number	Proposed Revision	Rationale
1651	Delete the footnote, or revise to say the ICH stability are the primary reference sources. This reviewer disagrees with the commenter's remarks.	Regulators and industry have worked very hard to develop guidelines the ICH guidelines. FDA guidelines should not supersede them. FDA guidelines should only address areas not covered by ICH or that are unique to the U.S. First, if the Agency were to issue guidelines, they would supersede any guidance – because they are legally binding on both the industry and the Agency, the FDA does not currently issue guidelines, Knowing that the **FDA** understands better than this reviewer what it can and should do with respect to the ICH guidances, this reviewer will defer to their judgment and, barring an Agency-initiated change, this text should be left as it is in the final CMC guidance.
1793	Delete "Phase III Clinical".	The regulations require that EPRs be provided for bioavailability, bioequivalence and primary stability lots, not Phase III Clinical lots.
1817-1819	Delete the sentence that starts "This should include ...". This reviewer knows that this draft text or, should it come to exist, an improved version thereof should be incorporated into the final CMC guidance.	Provision of duplicate CofAs is unnecessary. Comparison of supplier and applicant data is a GMP issue and can be addressed by the inspector if appropriate. While this reviewer agrees that providing "duplicate CofAs is unnecessary," this text makes no such request. Since the Agency is charged with a duty to ensure that the manufacturing, controls, and drug products are **CGMP** compliant, and the commenter admits that this comparison "is a GMP issue" that "can be addressed by the inspector," then it is also an application review issue that can be addressed by requesting the applicant to provide the requisite information.
1893	Add after included "if packaged in single unit containers.". This reviewer cannot agree with this reviewer.	Uniformity of dosage unit is applicable to individual dosage units. This reviewer knows that it is important for the semisolids that the manufacturers determine the uniformity regardless of the packaging. This is the case because this reviewer has been involved in several product investigations involving hydrocortisone creams and triple antibiotic ointments. The problem in all but one case was significant non-uniformity across the batch in the filled tubes. Obviously, this information should be submitted. The draft text should be retained, if nothing else, because the commenter has failed to present any rationale, much less a substantive scientifically sound rationale, for the change the commenter has proposed.

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

Paul G. King Consulting's Submission Posted May 20, 2003 To Docket 02D-0526: "C-01"

Note: The original INTRODUCTORY 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 quoting from the **USP**, a Times New Roman font will be used. In this review, this reviewer's comments are made after the commenter's remarks and, when the commenter's remarks are "boxed," are placed inside the box.

These comments begin with "The comments being provided to Docket: "**02D-0526**" are based on a second reading and review of "**Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information; Availability** [G:\1215dft.doc – 12/16/02]" that attempts to add elements that connect various issues in the draft provided by the Agency to the CGMP regulations upon which they are supposed to be based. The current comments embody slight revisions and grammatical corrections from the original comments submitted earlier (posted on 8 April 2003)."

1 Page 9

Line "331" – "In general, a fixed amount for each component should be stated." **should be revised to read as follows:**

Except for the active ingredients and the filler or diluent used to balance the change in the weight of the weight of each "Drug substance" needed to ensure that the requirements of **21 CFR 211.101(a)** *are met*, a fixed amount for each component should be stated.

[**Notes:** To satisfy the requirements of **21 CFR 211.101(a)**, the amount of active should be determined by adding a small amount over the label claim (typically, 0.5 % to 1 %, or, if there are significant losses in processing, 0.5 % more than the worst-case processing loss) to the label claim amount and then dividing that weight by the "as is" weight-fraction **purity** of active in the lot or batch of the active pharmaceutical ingredient (API; "Drug substance") assigned to be used in a given batch of the drug product. The resulting weight should be rounded to the nearest 0.01 % of the weight calculated. Then, the weight of the largest "Filler" or "Diluent," or the one first blended with the drug substance should be appropriately reduced so that the weight of the drug substance plus that filler or diluent is a constant. For example, IF: **a)** the label claim is 1 mg, **b)** the firm adds a 1% overage, and the weight-fraction purity of the lot of API to be used is 0876, THEN, the formulation would need to be adjusted to 1mg x 1.01/0.876 = 1.152968037 or, rounding to the nearest "0.01 %," 1.153 mg. Then, 0.153 mg should be appropriately subtracted from the weight of the appropriate "Filler" or "Diluent."]

In general, this reviewer agrees with the commenter's proposed revision but would modify it slightly to read:

"Except for the active ingredients and the filler or diluent used to balance the change in the weight of the weight of each 'Drug substance' needed to ensure that the requirements of **21 CFR 211.101(a)** *are met*, a fixed amount for each component should be stated. In cases where the applicant is required to adjust the weight of the active or actives or can justify a range for the weight of some other component, the total weight in the portion of a defined formulation containing the actives should be a constant."

2 **Page 10**

Comments On "**Table 1**" at **Line** "**358**"

2.1 First the weights in the table should be uniformly expressed for each ingredient as shown in the **"Revised Table 1"** shown on the next page.

2.2 The weight of the "Drug substance" needs to be more than 100 % of the label claim to meet the requirements set forth in **21 CFR 211.101(a)**, "The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient." To do this a slight overage must be added and the drug substance must then be corrected for its "as is" fractional weight purity. **[Note: 21 CFR 211.84(d)(2)** requires the purity of components to be determined, "Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality."]

2.3 Strictly, "**Excipient X**" is a "Filler" and not a "Diluent" because the term "diluent" applies to components that dilute actives by some integer multiple. Moreover, the level of this "Filler" must be reduced by the amount the correction for purity increases the weight of drug substance so that the total "Core Tablet Weight" is maintained without changing the level of disintegrant, binding agent or lubricant.

2.4 The changes proposed in "**Table 1**" are in a **bold** font.

This reviewer agrees with all that is said except that in commenter's "2.3" the text, "**Excipient X**" is a 'Filler' and not a 'Diluent' because the term 'diluent' applies to components that dilute actives by some integer multiple," could be better stated as, "**Excipient X**" is a 'Filler' and not a 'Diluent' because the term 'diluent' ~~applies to components that~~ **should be restricted to instances where the component** dilute actives by some ~~integer~~ multiple of the actives' level."

"Revised" Table 1: Example Target Composition Statement

Component Referenced	Quality Standard	Function	50 mg Tablet	100 mg Tablet	150 mg Tablet
Core Tablet					
Drug substance	In-house standard	Drug Substance	**55.55 mg[1]**	**111.00 mg[1]**	**166.65 mg[1]**
Excipient X	NF	~~Diluent~~ **Filler**	**28.45 mg[2]**	**59.00 mg[2]**	**88.35 mg[2]**
Excipient Y	NF	Disintegrant	22.0 mg	44.0 mg	66.0 mg
Excipient Z	In-house standard	Binding Agent	5.0 mg	10.0 mg	15.0 mg
Magnesium Stearate	NF	Lubricant	1.5 mg 3	.0 mg	4.5 mg
Core Tablet Weight			113.5 mg	227.0 mg	340.5 mg
Film Coat Solution					
Purified Water	USP	Processing Agent	—	—	—
Hydroxypropyl Methylcellulose	USP	Film Coat	4.5 mg	9.0 mg	13.5 mg
Color Red™[3]	DMF Holder Y standard	Film Coat Color	—	0.20 mg	—
Color Blue™[3]	DMF Holder Y Standard	Film Coat Color	0.05 mg	—	0.45 mg
Titanium Dioxide	USP	Opacifier	0.10 mg	0.10 mg	—
Total Tablet Weight			118.15 mg	236.30 mg	354.45 mg
Print Ink Solution					
Printing Ink Solution[4]	DMF Holder Z Standard	Identification	—	—	—

[1] Equivalent to 50, 100, and 150 mg, respectively, on the anhydrous basis – weight adjusted based on a processing overage of 1.0 % and corrected for purity by dividing resulting weight by "as is" fractional weight purity and rounding result up to nearest 0.01 mg. For example if the "as is" fractional weight purity is 0.987 %, and the active is to be formulated as a 100 mg tablet, the drug substance amount would be 112.45 mg.

[2] **The weight of filler is adjusted by subtracting the extra weight of Drug Substance added from the nominal fill weight in order to keep the total weight constant. In the example shown, an extra 1.45 mg of Drug Substance would reduce the weight of "Filler" from "59.00 mg" to "57.65 mg."**

[3] The qualitative and quantitative composition statements for the two colors are incorporated by reference from DMF 99999. The information is located in the January 21, 2001 amendment to the DMF, Volume 2, page 104 and 105. See the letter of authorization from DMF Holder Y in Module 1.

[4] The qualitative and quantitative composition of the ink is provided in Table XYZ in the application.

This reviewer concurs with the changes proposed in this table.

3 Page "10"

Lines "364 – 367," "The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application." **should be revised as follows:**

The Pharmaceutical Development section should contain information on the development studies conducted to establish that:

a) *Components, and their identity, purity, quality and control specifications,*
b) *Dosage form and its statistical-quality-control-based batch-release specifications,*
c) *Formulation and the overages of actives added,*
d) *Manufacturing process and its representative-sample-based in-process control specifications,*
e) *Container-closure system and that system's acceptance and performance specifications,*
f) *Microbiological attributes, including, as appropriate, viral, and/or endotoxic attributes, and*
g) *Usage* instructions

are *scientifically sound and* appropriate for the purpose specified in the application.

[Notes:

"a)" Component **identity, purity, quality"** is required to satisfy **21 CFR 211.84** and "component **control specifications"** are required to satisfy **21 CFR 211.110.**

"b)" Dosage-form **statistical-quality-control-based release specifications** are required to satisfy **21 CFR 211.165** (specifically, **21 CFR 211.165(d)** and, for dosage forms containing ingredients that control (accelerate or retard) drug availability, **21 CFR 211.167(c).**

"c)" Component **overages are required for the active ingredients to meet** the "provide not less than 100 percent" **requirement of 21 CFR 211.101(a).**

"d)" Representative-sample **in-process testing is required** "at commencement or completion of significant phases" **(21 CFR 211.110(c))** "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" **(21 CFR 211.110(a)).**

"e)" Container-closure system's **acceptance and performance specifications are required** to satisfy **21 CFR 211.84** and the implicit requirements of **21 CFR 211.130** governing "Packaging and labeling operations."

"f)" The phrase **"including, as appropriate, prionic, viral, and/or endotoxic attributes"** should be added to ensure that such are considered and, where such can affect product safety, reflected in the submission documents.

"g)" "are **scientifically sound and** appropriate" – **21 CFR 211.160,** "... controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity," requires all controls to be, first, **scientifically sound** and, second, appropriate – not just "appropriate" as the text currently reads.]

This reviewer agrees with the comments made.

4 Page "10"

Lines "367 – 368," "The studies included in this section are distinguished from routine control tests conducted according to specifications (e.g., release testing, stability testing)." **should be revised as follows:**

The studies included in this section are distinguished from routine control tests conducted according *to the scientifically sound and appropriate* specifications (e.g., *incoming testing, in-process testing,* release testing, and stability testing) *derived from the results found from the testing of the appropriate full-scale batch- or lot- representative samples during the final stages of development.*

This reviewer concurs.

5 **Page "11"**

Lines "369 – 371," "Additionally, this section should identify and describe the formulation and process attributes, including critical parameters, that can influence batch reproducibility, product performance, and drug product quality." **should be revised as follows:**

"Additionally, this section should identify and describe the *component,* formulation and process attributes, including critical parameters, which can influence batch reproducibility, product performance, and drug product quality."

This reviewer concurs; the impacts of the properties of the components on the manufacturing reproducibility and drug product quality should be addressed.

6 **Page "11"**

Lines "383 – 390," "Key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic form, solvation or hydration state, pH, dissociation constant (pKa)) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed. If the drug substance is structurally modified from an active moiety (e.g., salt, endogenous protein) and the modification affects a key physicochemical (e.g., solubility) and/or biological characteristic, this should be discussed. These discussions should cross-reference any relevant stability data in S.7.3)." **should be revised as follows:**

"Key physicochemical characteristics (e.g., water content, solubility, particle size distribution, *bulk and tap density, flow, surface affinity, hardness,* polymorphic form, solvation or hydration state, pH, dissociation constant [pKa]) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed. If the drug substance is structurally modified from an active moiety (e.g., salt, endogenous protein) and the modification affects a key physicochemical (e.g., solubility) and/or biological characteristic, this should be discussed. These discussions should cross-reference any relevant stability data in S.7.3)."

This reviewer concurs; physical properties other than "**particle size distribution**" are important and need to be mentioned.

7 **Page "14"**

Lines "511 – 512," "Data to support scoring should include content uniformity and dissolution studies comparing split versus whole tablet.[12]" **should be revised as follows:**

Data to support scoring should include *batch-representative* content uniformity and dissolution sample studies *comparing the batch active-uniformity and batch active-release properties of the split tablet fractions to the corresponding batch-representative samples of the* whole tablet.[12]

This reviewer would revise the commenter's proposal to read:

"Unless the tablet scoring is used purely as an identifying feature and the tablet labeling states that the tablet is not to be broken, ~~Data~~ **data** to support scoring should include *batch-representative* content uniformity and dissolution sample studies *comparing the batch active-uniformity and batch active-release properties of the split tablet fractions to the corresponding batch-representative samples of the* whole tablet.[12]

8 **Page "14"**

Lines "521 – 524," "The amount of overfill should be sufficient to ensure that the finished dosage form meets appropriate pharmacopeial tests (e.g., *United States Pharmacopeia* (USP) *General Chapters* <1> *Injections*, <698> *Deliverable Volume*, <755> *Minimum Fill.*" **should be revised as follows:**

Full-scale-batch-representative sample testing should be used to establish that the minimum specified overfill is sufficient to ensure that *each and every article of the finished dosage form in that the batch* meets *the minimum CGMP batch-acceptance requirements set forth in* **21 CFR 211**, *and, if tested, will meet* the appropriate pharmacopeial tests (e.g., *United States Pharmacopeia* (USP) *General Chapters* <1> *Injections*, <698> *Deliverable Volume*, <755> *Minimum Fill.*

This reviewer concurs, but would correct "<755> Minimum Fill" to "<755> Minimum Fill**).**" and add the following sentence:

"In cases where no full-scale batches have been produced, the results from the testing of the largest scale batch having the same formulation as the proposed formulation should include the testing of the lesser of: **a)** twice the number of batch-representative units that compliance with ***ISO 3951*** (or the equivalent American National Standard, ***ANSI/ASQ Z 1.9***) would require, or **b)** at least three times the number of batch-representative required by those standards for the size of that largest scale batch."

9 **Page "14"**

Lines "531 – 537," "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., compensate for expected and documented manufacturing losses, ensure proper dose delivery), and (3) 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)." **should be modified as follows:**

An overage is a fixed amount of the drug substance *(active ingredient)* 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, *<u>including</u> the overage added to satisfy the requirement set forth in* **21 CFR 211.101(a)**. Information should be provided on the: (1) amount of overage, (2) reason for overage (e.g., compensate for expected and documented manufacturing losses, ensure proper dose delivery), and (3) 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).

[Note: For overages arising from the variation in the weight of the "less than 100 % pure" API necessary to provide the required weight of active ingredient (drug substance) in the formulation, the amount of API listed in the composition statement (P.1) and the representative batch formula (P.3.2) needs to be appropriately increased based on the weight-fraction "purity" of the active ingredient (drug substance) in the API.
The formula for computing the required weight of each API should be:

(Required weight of active ingredient) / (weight-fractional purity of the API)

It is neither scientifically sound nor appropriate to use "100 %" divided by the Assay in place of the weight-fraction purity ("100 %" divided by the weight-percent purity). This is the case because the reported "Assay" of a given lot of API is NOT a valid measure of the purity of that lot of API. This is the reason **21 CFR 211.84(d)(2)** specifically requires, "Each component shall be tested for conformity with all appropriate written specifications for <u>purity</u>, strength, and quality." *This is the case because API purity is not the same as API strength (typically measured by an Assay).* In addition, the weight of the appropriate "Filler" or "Diluent" in the

composition statement (P.1) and the representative batch formula (P.3.2) needs to be reduced by the additional weight of API required.]

This reviewer concurs.

10 **Page "14"**

Lines "638 – 640," the indent "• for sterile products, the integrity of the container closure system as it relates to preventing microbial contamination" **should be followed by:**

- *For protein-based components and products derived from animal sources, the proof that such products are free of prionic contamination including any transmissible spongiform encephalopathy (TSE)*
- *For components and products derived from animal tissues subject to contamination by viruses, the proofs that such product are free of viral contamination*
- *For components and products that may contain endotoxins, the nature and level of such contaminants in such components and products and the pathways and levels of reduction by which are reduced to acceptable levels in the finished drug product.*

In general, this reviewer concurs but would recommend changing the phrase "free of viral contamination" to free for **adventitious** viral contamination."

11 **Page "20"**

Lines "765 – 767," "Explanatory notes should be included as appropriate. For example, explanatory notes should be used to identify components that are removed during processing or the purpose of inert gases used during the manufacturing process." **should be revised to read:**

Explanatory notes should be included as appropriate. For example, explanatory notes should be used to:

- *Explain the adjustment of the weight of API required to ensure that the weight of active ingredient (drug substance) added is sufficient to meet the requirements of* **21 CFR 211.101(a).**
- *Explain the adjustment of the weight of the "Filler" or "Diluent" reduced to ensure that the total formulation weight is of the active ingredients plus the adjusted "Filler" or "Diluent" weight is a constant.*
- *Identify* components that are removed during processing or the purpose of inert gases used during the manufacturing process.

This reviewer concurs.

12 **Page "21"**
Lines "769 – 770," "Table 2" should be revised as follows:

Table 2: Proposed Batch Formula[1] — 250 mg Trademark™ Tablets		
Core Tablet		
Component	Reference to Quality Standard	Amount (kg **or** L) per batch
Drug Substance	In-house Standard	**505.0 kg**[2]
Excipient X	**National Formulary (NF)**	**305.0 kg**[3]
Excipient Y	NF	**280.0 kg**
Excipient Z	In-house standard	**50.0 kg**
Magnesium Stearate	NF	**15.0 kg** (range 14.5 to 15.5)
Purified Water	**United States Pharmacopeia (USP)**	(200 L)[4]
Total Batch Size		**X**
Film Coat Solution[5]		
Component	Reference to Quality Standard	Amount (kg or L) per batch
Hydroxypropyl Methylcellulose	USP	**10.0 kg**
Purified Water	USP	(200 L)[4]
Color Red™	DMF Holder Y Standard	**10.0 kg**
Color White™	DMF Holder Y Standard	**1.5 kg**
Total Batch Size		**Y**
Print Ink Solution		
Colorant™	DMF Holder Z Standard	0.15 **kg**
Solvent	NF	(10 L)[6]
Total Batch Size		**Z**

[1] Theoretical yield is 2,000,000 tablets **based on a 250 mg tablet weight and a 1 % formulation overage added to ensure that the "not less than 100 percent" requirement of 21 CFR 211.101(a) is met.**
[2] **The actual amount of API to be weighed out for a given lot of API is given by the formula: 505.0 kg/(API Lot's weight-fraction purity) with the result rounded to the nearest 0.1 kg.**
[3] **The actual amount of "Excipient X" to be weighed out is 305.0 kg minus (API kg weight computed in Footnote 2 minus 505.0 kg).**
[4] Water is removed during processing.
[5] Film coat weight may vary between 80% **and** 120% of target coating weight.
[6] **Solvent evaporates after ink is applied.**

[**Note:** The rationale for the preceding changes (in **bold**) should be self-evident. However, the proposed changes are required:

1. To ensure that **21 CFR 211.101(a)** is met,a n overage must be added for the active ingredient. The "1 %" value was selected because this is the typical minimum value that permits a valid (*scientifically sound and appropriate*) determination of the *batch strength* (*as required by* **21 CFR 211.165(a)**, "For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to

release. ...") based on the "Assay" testing of a "few" (< 20 at the 95 % confidence level) aliquots from an appropriately homogenized *batch-representative* composite sample.

2. To ensure that the weight of a given lot of API added to this formulation is sufficient to provide the required weight of active ingredient, the API weight must be adjusted by dividing the nominal weight required by the weight-fractional "purity" of the API with respect to the active. This is required because no API is 100 % pure by weight; typically, the "active" purity of most APIs is less than 99 % and, in some instances (where the active is purchased diluted in a carrier) may be as little as 1 % of the component's weight.
3. To ensure that the overall weight of the formulation is approximately constant, the weight of some "excipient" that does not affect active availability (a filler or a diluent) must be reduced in weight by the amount added by the adjustment of the weight of the API required.

The weights of materials added by weight in the formulation table should be expressed to the level precision that the balance used to weigh them. For ingredients dispensed by volume rather than weight that do not remain in the formulation after the completion of the processing steps that add them, the volume (weight) added need only be expressed to the nearest liter (kilogram) unless less than a liter (or kilogram) is to be added (in such cases, the volume [weight] added should be expressed to the nearest 0.1 L [0.1 kg]).

This reviewer concurs.

13 Page "21"

Lines "774 – 776," "The description of the manufacturing process and process controls should include a flow diagram of the manufacturing process and a detailed description of the manufacturing process and process controls." **should be revised to read**:

The description of the manufacturing process and process controls should include:

- *Flow* diagram of the manufacturing process,
- *Detailed* description of the manufacturing process, and
- *Detailed description of the* process controls *that includes the rationale that establishes that the process controls specified satisfy: a) the in-process controls* (**21 CFR 211.110** and **21 CFR 211.160**) *and b) the batch release controls* (**21 CFR 211.160**, **21 CFR 211.165**, and **21 CFR 211.167**) *set forth in the minimum CGMP regulations for finished pharmaceuticals* (**21 CFR 211**).

This reviewer concurs; the CGMP manufacturing process begins with the proper control of incoming materials (components, containers, closures, labeling, packaging, and process auxiliaries) and only ends when the approved finished packaged drug product batch leaves the manufacturer's control.

14 Page "26"

Lines "948 – 950," "When the same analytical procedure is used for both the in-process test and the finished product test, the acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the finished product specification." **should be revised to read**:

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 variability 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, or, when subsequent in-process steps are known to improve batch uniformity, appropriately wider than the acceptance criterion in the finished product specification.

This reviewer concurs.

15 Page "28"

Lines "1024 – 1026," "At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1))." **should be revised to read:**

At a minimum, the drug product manufacturer must perform an appropriate identification test *and, if specific identity tests exist, they must be used* (**21 CFR 211.84(d)(1)**, "At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used."). *Moreover, all testing must be performed on a batch-representative set of samples* (**21 CFR 211.160(b)(1)**, "Laboratory controls shall include: (1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. ..."). *In addition, the drug product manufacturer must appropriately determine the purity, not the Assay, of each shipment of each lot of component that has a discrete chemical composition. Each purity determination must be performed on an appropriate batch-representative sample from the lot tested.*

In general, this reviewer concurs, but notes that the phrase "**an appropriate identification test**" should, at a minimum, be changed to "**an appropriatei ~~dentification~~ identity test**" to make it fully compliant with the **CGMP** requirements for components or, as the reviewer has noted in the review of the PhRMA comments, more properly, the cite should be changed to **21 CFR 211.84(d)(2)** because, as the regulatory text is constructed, **21 CFR 211.84(d)(1)** only applies when the manufacturer is doing full testing.

If the manufacturer elects to use a report of analysis (or certificate of analysis) from the component's manufacture, then **21 CFR 211.84(d)(2)** applies and the true minimum becomes the minimum established in **21 CFR 211/84(d)(2)**.

Based on the preceding regulatory reality, this reviewer recommends that the text in the guidance be changed from, "**At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1))[27].**" to "**At a minimum, the drug product manufacturer must perform at least one specific identity test (21 CFR 211.84(d)(2).**"

15 Page "29"

Lines "1053 – 1057," "When the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, a statement indicating the analytical procedure and reference can be provided rather than the analytical procedure itself." **should be revised to read:**

When the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, *enhanced, or itst ext changed in any way*, a statement indicating the analytical procedure and reference can be provided rather than the analytical procedure itself. *If the firm's implementation of an analytical procedure changes it in any way from the current FDA-recognized revision, the firm must include a copy of its analytical procedure in its filing.*

This reviewer concurs.

16 **Page "29"**

Lines "1062 – 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 that are interchangeable with a USP *General Chapter*) are used, they should be verified to be suitable under actual conditions of use." **should be revised to read:**

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 that are interchangeable with a USP *General Chapter*) are used *without any modification, change, augmentation or interpretive language*, they should be verified to be suitable under actual conditions of use. *Otherwise, such analytical procedures must be appropriately validated.*

While this reviewer thinks that the commenter's suggestion is a good, this reviewer thinks that, to enhance this guidance's immunity to the need for technical revisions caused by agencies outside of the control of the **FDA**, the commenter's text should be further revised to:

"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 *without any modification, change, augmentation or interpretive language*, they should be verified to be suitable under actual conditions of use. Otherwise, such analytical procedures ~~must~~ **should** be appropriately validated."

This reviewer understands and agrees with the commenter's need for the restrictive language, "are used *without any modification, change, augmentation or interpretive language*," on what constitutes an analytical procedure from an FDA-recognized source but knows that the inclusion of the restrictive phrase, "that are interchangeable with a General Chapter," is more restrictive than the underlying regulation's language and therefore should not be included in this guidance document.

Similarly, the use of the word "must" should, in general, be avoided in guidance because: **a)** its use is inappropriate therein and **b)** those in the industry to whom it is directed are responsible for knowing and doing what the minimums in the underlying regulations require of them.

17 **Page "30"**

Lines "1079 – 1081," "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)." **should be revised to read:**

For compendial excipients, justification of *the scientific soundness and appropriateness of* the acceptance criteria for tests beyond those included in the monographs *or required in* **21 CFR 211.84** is *required* (e.g., particle size, flow properties, impurities).

This reviewer concurs with the revision suggested but notes that its grammatical construction is awkward.

18 **Page "30"**

Lines "1093 – 1094," "Use of terms such as *conforms* or *meets specification* is discouraged." **should be revised to read:**

Use of terms such as *"conforms"* or *"meets specification"* is *proscribed.*

This reviewer disagrees, but, to address the commenter's genuine concerns, proposes to revise the guidance sentence to read, "**Use of terms such as *conforms* or *meets specification* 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*.**"

19 **Page "31"**

Lines "1100 – 1106," "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.* Use of terms such as *conforms* or *meets specification* is discouraged." **should be revised to read:**

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 *(or materials from other susceptible herbivores)*, 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.*

This reviewer concurs with the minor changes proposed.

20 **Page "31"**

Lines "1108 – 1110," "The potential adventitious agents should be identified, and general information regarding control of these adventitious agents (e.g., specifications, description of the testing performed, and viral safety data) should be provided in this section." **should be revised to read:**

The potential adventitious agents should be identified, and general information regarding control of these adventitious agents (e.g., specifications, description of the testing performed, and viral *and prion* safety data) should be provided in this section.

This reviewer agrees with the text added by the commenter.

21 **Pages "31" to "32"**

Lines "1133 – 1142," "The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. They are proposed and justified by the manufacturer and approved by the Agency. Specifications are established to confirm the quality of drug products rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Information on periodic quality indicator tests is provided below." **should be revised to read**:

The proposed specification for the drug product *batch* should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *"Conformance to specification"* means that *batch representative samples from* the drug product *batch*, when tested according to the listed analytical procedures, will meet conform to the drug product CGMP requirements established in **21 CFR 211.110, 21 CFR 211.160, 21 CFR 211.165** and, where applicable, **21 CFR 211.167** and the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. *The manufacturer proposes and justifies their scientific soundness, appropriateness, and conformance to the applicable CGMP requirements for the drug product batch. If and only if the Agency finds that the specification proposed complies with said CGMP requirements, the Agency can then approve it for use. [**Note:** As per a 1988 U. S. Supreme Court ruling (**Berkovitz v. US** {**486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**}), the Agency has no authority to approve specifications that do not comply with any of the clear requirements set for in* **21 CFR 211**.*]* Specifications are established to confirm the quality of drug product *batches based on the results obtained from the testing of batch-representative samples therefrom* rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety *(as measured by the batch's drug product identity, strength, and levels of the impurities)* and efficacy *(as measured by the batch's uniformity with respect to the active and the active release or release rate)*. Information on periodic quality indicator tests is provided below.

This reviewer supports the changes and additions made, and knows that these should: **a)** help the industry to understand what the regulations require of them in this area as well as: **b)** reduce the Agency's risk that they may approve an application that is violative in the cited areas of the CGMP regulations.

22 **Page "32"**

Lines "1144 – 1162," "The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))

- all analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30]
- acceptance criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC).
- release and shelf-life acceptance criteria when both are used.

The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. They are proposed and justified by the manufacturer and approved by the Agency. Specifications are established to confirm the quality of drug products rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Information on periodic quality indicator tests is provided below." **should be revised to read:**

The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria *for the batch-representative samples tested (as* **required by 21 CFR 211.160(b)(3)***) and the calculated batch statistical quality control values derived from the batch-representative sample results* (as required by **21 CFR 211.165(d)**). *The specification sheet* should also include a reference to the analytical procedures that will be used to perform each test and the recognized statistical standard used to evaluate the statistical acceptability of the batch. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- *Tests* that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))
- *All* analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30]
- *Acceptance* criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC).
- *Release* and shelf-life acceptance criteria, when both are used.

The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. They are proposed and justified by the manufacturer and approved by the Agency. Specifications are established to confirm the quality of drug products rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy.Inf ormation on periodic quality indicator tests is provided below."

In general, this reviewer concurs but notes that the added paragraph needs to be included in the revision for completeness.

23 Page "32"

Lines "1164 – 1170," "The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that should be included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there are sufficient data and justification. Recommendations on tests for other dosage forms are included in Attachment 1." **should be revised to read:**

The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that *can be used as the basis for the tests to be* included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there *is* sufficient data *to support such periodic rather than each batch evaluation provided the firm can demonstrate CGMP compliance without performing such tests on every batch. In general, the tests amenable to such treatment are those that evaluate factors, like appearance, that have no direct bearing on the safety and efficacy of the drug product. In general, the CGMP for drug product (finished pharmaceuticals;* **21 CFR 211**) does not permit omitting tests that bear on the identity, purity, strength and performance quality of the each drug batch. Recommendations on tests for other dosage forms are included in Attachment 1."

This reviewer concurs, but would propose the following slightly revised text: "The ICH guidance ***Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*** **provides recommendations on tests that *can be used as the basis for the tests to be* included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there ~~are~~ is sufficient data ~~and justification.~~** to support such periodic rather than each batch evaluation **provided** the firm can demonstrate CGMP compliance without performing such tests on every batch. In general, the tests amenable to such treatment are those that evaluate factors, like appearance, that have no direct bearing on the safety and efficacy of the drug product as well as those tests that are beyond the **CGMP** minimums, like in-process statistical process controls and control charting. In general, the **CGMP** for drug product (finished pharmaceuticals; **21 CFR 211**) does not permit omitting tests that bear on the identity, purity, strength and performance quality of the each drug batch. **Recommendations on tests for other dosage forms are included in Attachment 1."**

24 **Pages "32" – "33"**
Lines "1172 – 1175," "An illustrative example of a specification sheet is provided in Table 3." ➔ **"Table 3"**

1 The example provided in **Table 3** is deficient in several aspects including, failure to: **a)** specify that the sample tested must be batch representative, **b)** specify the number of sample units that must be tested for batch acceptance, **c)** specify if the tests should be on each unit or on a homogeneous composite (and if on the composite, how many aliquots).

2 In addition, as most do, the example confuses specification limits appropriate to a given post-release grab-sample test (the **USP** test for an *article*) with specifications appropriate to batch acceptance or rejection for the appropriate testing of a batch-representative sample.

3 Finally, though appearance testing using **ANSI Z 1.4** (or the obsolete Mil Std 105E or 105F) is an integral part of the testing used by a firm for batch acceptance, no mention is made of it in the example table.

4. For compliance with **21 CFR 211.165(d)**, the reference standard **ISO 3951**:1989 and its acceptance criteria need to be addressed when statistical quality control acceptance decisions are to be made (typically required for active uniformity ("content uniformity") and the uniformity of the release ("dissolution") or the rate of release ("drug release") of the active ingredient

To address the preceding issues, the following alternate **Table 3**, shown on the next three pages, is proposed.

This reviewer concurs

25 **Page "33"**
Lines "1178 – 1181," "The CGMP regulations require that for each batch of drug product, there will be appropriate laboratory determination of satisfactory conformance to the drug product specification. Drug product failing to meet established standards or its specification and any other relevant quality control criteria must be rejected (21 CFR 211.165)." **should be revised to read:**

For each batch of drug product being evaluated for acceptance, the CGMP regulations require:

- The sampling and examination or testing of batch-representative samples (**21 CFR 211.160(b)(3)**).
- The laboratory evaluations to be performed on said batch-representative samples to establish the satisfactory conformance of said samples **"to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release" (21 CFR 211.165(a))**.
- Appropriate **"laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms" (21 CFR 211.165(b))**.
- **Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed (21 CFR 211.165(c))**.
- 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 (**21 CFR 211.165(d)**).
- **The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented (21 CFR 211.165(e))**.
- **Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected** (**21 CFR 211.165(f)**).

This reviewer concurs

Table 3: Specification for Trademark™ Tablets (100 mg [1])				
Property Being Evaluated	**Representative Sample Number And Protocol (Individual {RI-N} or Homogeneous Composite [with testing of "n" aliquots] {HC-N-n})**	Acceptance Criteria	**Regulatory Analytical Procedure**	**Alternative Analytical Procedure**
Description	RI – 800 **(normal inspection)** [RI – 125 (reduced inspection)]	White, biconvex, 11-mm diameter, 4-mm thick, film-coated tablet, with "identifier code XYZ" on one side.	**Visual**	
Appearance		0 [0] **Broken**; NMT[2] 5 [1] **Chipped**; NMT 7 [1] **Film holes/bubbles**; NMT 21 [5] **Other minor visual defects**	**ANSI Z 1.4 Normal Inspection: Single Level 0.015, 0.25 & 1.5 %**	**ANSI Z 1.4** Reduced: Inspection: Single Level Same %
Dimensions/Hardness		10.5 – 11.5 mm in diameter 3.9 – 4.5 mm thick	**AP [3] # DIM3A**	**AP # ADM09**
Core Weight and Core Hardness[4]	**RI – 9 or more sets of 23 tablets** (1 from each of 23 stations in tablet press used)	**Weight** / **Hardness** Setup Target: 443 mg NLT[5] 9.5 KP[5] Setup Mean: NLT 442 mg NLT 10.2 KP Setup Range: 440 – 446 mg 8.7 – 12.5 KP Run Range: 437 – 449 mg 7.5 – 14.0 KP Run Mean: NLT 440.5 mg NLT 9.0 KP	**AP # WTS4B**	**AP #AWT11**
Identification Test #1	**HC-200-1**	Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the USP-based Assay.	**HPLC, AP # EFG2**	**AP # UVR19**
Identification Test #1	**HC-200-1**	Responds to the tests for sulfate	**USP <191>**	
Active Uniformity in the Tablets (AUT) - Content Uniformity (CU)	**RI – 200** (normal test) [RI – 75 (reduced test)]	**§§ 211.101(a) Compliance** (Release) **Mean ($\bar{X}$): NLT 100.2 LC[6] (200);** [NLT 100.0% (75)] **§§ 211.110 Compliance** (Release) **Range: 90 – 112 % LC; RSD: ⩽ 3.7 %** [92 – 110 % LC; RSD: ⩽ 4.0 % **§§ 211.165(d) Compliance** (Release) **SQC Acceptance Using ISO 3951** **The "s" method, n = 200, AQL 0.1 %** **Accept: ($\lvert 112 - \bar{X} \rvert / s$) & ($\lvert \tilde{X} - 90 \rvert / s$) ⩾ 2.73** ."s" method, n = 75, AQL 0.1 % Accept: ($\lvert 112 - \bar{X} \rvert / s$) & ($\lvert \tilde{X} - 90 \rvert / s$) ⩾ 2.55 **USP Compliance** (Lifetime) NONE outside of 75 – 125 % of LC, NMT 1 in 30 outside of 85 – 115 % of LC RSD NMT 7.8; Mean NLT 95 % LC	**HPLC, AP # EFG2** **HPLC, AP # EFG1**	**AP # UVS29**
	Post-Release **USP Article 30**			

Table 3: Specification for Trademark™ Tablets (100 mg [1]) [Continued]				
Property Being Evaluated	**Representative Sample Number And Protocol (Individual {RI-N} or Homogeneous Composite [with testing of "n" aliquots] {HC-N-n})**	Acceptance Criteria	**Regulatory Analytical Procedure**	**Alternative Analytical Procedure**
Active Availability Stage 1 [7]	**RI – 60** (correlated normal test) [RI – 42 (correlated reduced test)] (Release)	**§§ 211.110 Compliance** (Release) **Mean: NLT 85 % LC (60)** [NLT 85.5 % LC (42)] **Range: 78 – 97 % LC (60)** [80 – 95 % LC (42)] **§§ 211.165(d) Compliance** (Release) **SQC Acceptance Statistical Inference Using "s" Approach, n = 60, AQL 0.4 %** **Accept: ($\lvert 97 - \bar{X} \rvert / s$) & ($\lvert \bar{X} - 78 \rvert / s$) ≥ 2.22** .Using "s" Approach, n = 42, AQL 0.4 % Accept: ($\lvert 95 - \bar{X} \rvert / s$) & ($\lvert \bar{X} - 80 \rvert / s$) ≥ 2.04	**AP # BCD2** **AP # BCD1**	**AP # UVS28**
	Post-Release **USP Article Dissolution on 6 units** (Lifetime))	**USP Compliance** (Lifetime) **None: LT[8] 80 % LC** (or MT[9] 100 % LC) **Mean NLT 85 % LC**		
Active Availability Stage 2	Post-Release **USP Article Dissolution on 12 units** (Lifetime)	**Release has NO intermediate Stage** **USP Compliance** (Lifetime) **None: LT 65 % LC** *(or MT 105 % LC)* **Mean NLT 80 % LC** (corrected)	**No Test Defined** **AP # BCD1**	**No Test** **AP # BCD1**
Active Availability Stage 3	**RI – 200** (correlated normal test) [RI – 75 (correlated reduced test)] (Release)	**§§ 211.110 Compliance** (Release) **Mean: NLT 85 % LC (200)** [NLT 85 % LC (75)] **Range: 75 – 100 % LC (200)** [77 – 98 % LC (75)] **§§ 211.165(d) Compliance** (Release) **SQC Acceptance Statistical Inference Using "s" Method, n = 200, AQL 0.4 %** **Accept: ($\lvert 100 - \bar{X} \rvert / s$) & ($\lvert \bar{X} - 75 \rvert / s$) ≥ 2.33** .Using "s" Method, n = 75, AQL 0.4 % Accept: ($\lvert 98 - \bar{X} \rvert / s$) & ($\lvert \bar{X} - 77 \rvert / s$) ≥ 2.12	**AP # BCD2** **AP # BCD1**	**AP # UVS29**
	Post-Release **USP Article Dissolution on 24 units** (Lifetime)	**USP Compliance** (Lifetime) **None: LT[8] 55 % LC** *(or MT[9] 110 % LC)* NMT 2 LT 65 % LC Mean NLT 80 % LC (corrected)		
Tablet Strength (Assay)	**RI – 200**[75] (mean from **ADT** test) **or** **HC-200-8** (test NLT 8 aliquots ex. HC-200)	**§§ 211.101(a) Compliance** (Release) **Mean: NLT 100.2 LC (200);** [NLT 100.0 % (75)] **– or –** **Mean: NLT 100.0 LC** (8 aliquots)	**Result from "ADT" Test** **HPLC, AP # EFG2**	**AP # UVS29**
	Post-Release **USP Article – Assay 20** (homogenize and test duplicate aliquots)	**USP Compliance** (Lifetime) **Mean: 90 – 110 % LC** (2 aliquots) **RSD: NMT 2.0 %**	**HPLC, AP # EFG2**	

Table 3: Specification for Trademark™ Tablets (100 mg [1]) [Continued]					
Property Being Evaluated	**Representative Sample Number And Protocol (Individual {RI-N} or Homogeneous Composite [with testing of "n" aliquots] {HC-N-n})**	Acceptance Criteria		**Regulatory Analytical Procedure**	**Alternative Analytical Procedure**
Water Content	**HC-200-3** Post-Release **USP Article – grab 20 units** (homogenize and test single aliquots)	**NMT 0.7 % by weight – RSD NMT 1 %** (Release) **NMT 1.0%** (Lifetime)		**USP <921>; Method Ic**	**AP # PQR7**
Degradation Products **Specified Degradation Products** **Degradant A:** **Degradant B:** **Degradant at RRT[10] XX** **Unspecified Degradation Product** **Individual Unspecified** **Total Degradation Products:**	**Release** **HC-200-3** (Take 200 batch-representative units and homogenize them; then, test 3 unit-dose aliquots, average the results & compute the RSD values. Batch is acceptable when all impurities meet the release criteria set.) **Lifetime** Post-Release **USP Article – grab 20 units** (homogenize & test single aliquot)	**Release** **NMT 0.3 %; RSD <4 %** **NMT 0.4 %; RSD <3 %** **NMT 0.2%: RSD <5 %** **NMT 0.07%; RSD <8 %** **NMT 1.0%**	**Lifetime** **NMT 0.5 %** **NMT 0.6 %** **NMT 0.3%** **NMT 0.1%** **NMT 1.5%**	**HPLC; AP # EFG2**	
Residual Solvent A	**Release: HC-200-2** **Lifetime:** Post-Release **USP Article – grab 20 units** (homogenize & test single aliquot)	**Release** **NMT 100 ppm; RSD: NMT 2 %**	**Lifetime** **NMT 200 ppm**	**GC; AP # XYZ31**	

1 This product contains a 1 % formulation overage to ensure that the "intent to provide not less than 100 % of the label claim or established amount" requirement set forth in **21 CFR 211.101(a)** is met.

2 NMT = not more than

3 AP = Analytical Procedure

4 The Core Weight and Hardness tests are performed "in process" as the tablet cores are being produced.

5 NLT = not less than

6 LC = label claim

7 The process is designed to pass at "**Stage** 1." However, if a batch in release testing or a post-release **USP** article fails to meet the "**Stage-1**" criteria and all valid results are within the appropriate release range for the batch (60 % to 110 % of label claim) or the **USP**'s lifetime limits that, for this product, requires all tablets to have a dissolution value that is NLT 55 % of LC and no more than 2 in 6 tablets tested are less than 65 %, then the test plan should revert to full-sample testing (200 for the release test and any "12" [6 more] and "24" [18 more] for the post-release **USP** test).

8 LT = less than

9 MT = more than

10 RRT = relative retention time

In general, this reviewer finds the proposed alternative example much more comprehensive and to the point than the original, and trusts the final guidance will include it.

26 Page "35"

Lines "1250 – 1260," "If the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient. [32] When a general chapter or monograph included in an official compendium or other FDA recognized standard reference allows for the use of more than one analytical procedure for a test, the specific analytical procedure that will be used should be cited here (P.5.2) and in the specification (P.5.1). For example, when using USP <921> *Water Determination,* the method should be specified (e.g., Method Ia). If an analytical procedure is based on one of these sources but has been modified, the analytical procedure should be provided." **should be revised to read:**

If the *exact detailed written* analytical procedure used: ***a)*** *is available In,* ***b)*** *has been copied verbatim from, and* ***c)*** *uses the exact equipment specified in* the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified *in any manner*, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient[32]. When a general chapter or monograph included in an official compendium or other FDA recognized standard reference allows for the use of more than one analytical procedure for a test, the specific analytical procedure that will be used should be cited here (P.5.2) and in the specification (P.5.1). For example, when using USP <921> *Water Determination,* the method should be specified (e.g., Method Ia). If an analytical procedure is based on one of these sources but has been modified *in any manner*, the *detailed written validated* analytical procedure *and its supporting validation report* must be provided.

In general, this reviewer concurs except that the added phrase "... must be provided ..." should be replaced with "... **should** be provided ..." because this document is guidance.

27 Page "37"

Lines "1307 – 1309," "Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged." **should be revised to read:**

Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *"conforms"* or *"meets specification"* is *proscribed. In addition, where the value reported is the average of several individual results, either an ordered list of all of the individual results that were used to compute the average or, if the distribution of the results is at least pseudo-Gaussian, the range, number of values, standard deviation, mode, and median values should also be reported. In cases where the distribution is non-Gaussian and an average is reported, in addition to the reported average, either an ordered list of values found, or the number of values, a value frequency listing and the range, mode and median of the data set should also be reported.*

This reviewer again disagrees with the change from "**discouraged**" to "proscribed" in the second sentence and again recommends keeping that word and adding the constraining text previously proposed by this reviewer at **Commenter's 18**.

The added information should help firms to report their results in a more uniform and informative manner that, unlike the common current practice of only reporting the average value unless more is required, is also scientifically sound and helpful to providing the reviewers a truer picture of the results found.

28 **Page "37"**

Lines "1330 – 1334," "Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay and impurities (e.g., degradation products, residual solvents) and should be considered for other tests such as water content." **should be revised to read:**

Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay, impurities (e.g., degradation products, residual solvents), *active uniformity, and the uniformity of either the active-release or the active-release-rate* and *the reporting of collated data* should be considered for other tests such as water content.

This reviewer concurs with the commenter's proposed changes.

29 **Page "40"**

Lines "1415 – 1427," "Justification for the proposed drug product specification should be provided. The justification should be based on relevant development data (P.2), standards in an official compendium, batch analyses (P.5.4), characterization of impurities (P.5.5), stability studies (P.8), toxicology data, and any other relevant data. The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. Data from the clinical efficacy and safety, bioavailability, bioequivalence, and primary stability batches and, when available and relevant, development and process validation batches should be considered in justifying the specification. If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug product at any particular site. Justification for an in-process test that is used in lieu of a finished product test should be included in P.3.4." **should be revised to read:**

Justification for the proposed drug product specification should be provided. The justification should be based on

- *Relevant* development data (P.2),
- *The distributional properties in the dosage units in each batch required to ensure that each batch: **a)** meets the applicable CGMP requirements and **b)** will, if tested, be found to consist of articles having the property that every article in the batch will, with a high degree of certainty, meet the applicable* standards in an official compendium
- Batch analyses (P.5.4) *that demonstrate the uniformity of the batch with respect to its critical distributional quality properties,*
- *Characterization* of impurities (P.5.5),
- *Stability* studies (P.8),
- *Toxicology* data, and
- *Any* other relevant data.

The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. Data from the clinical efficacy and safety, bioavailability, bioequivalence, and primary stability batches and, when available and relevant, development and process validation batches should be considered in justifying the specification. If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug product at any particular site. Justification, *including the*

rationale that clearly establishes that the proposed substitution complies with all of the applicable CGMP requirements set forth in **21 CFR 211**, for *any proposed* in-process test that is *to be* used in lieu of a finished product test should be included in P.3.4.

This reviewer finds the commenter's proposal to be a distinct improvement over the existing text.

In addition, the proposed text should assist the applicants in assuring that their justifications are truly scientifically sound and based on the results data from the testing of sufficient numbers of batch-representative samples.

If the applicants follow the guidance, then the review of their applications should be speeded by the lessened "data gathering and collation" workload on the PAI inspectorate.

30 Page "41"

Lines "1456 – 1459," "In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria." **should be revised to read**:

In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria *provided the applicable CGMP regulations do not explicitly require the test in question to be conducted on each batch.*[33]

This reviewer concurs with the commenter's suggested proviso.

In addition, this reviewer would like to remind the reader that, where warranted, those manufacturers whose drug products are well controlled and routinely produce drug product lots within limits tighter than those required for **CGMP** compliance should strongly consider using the well-defined inspection plans set forth in ISO that, if properly applied, permit some reduction in the number that are required for a valid test even in cases where the inputs (components and in-process materials) are not rigorously controlled.

31 Page "41"

Footnote "33," "[33] A proposal to drop a test, based on historical data, can also be submitted post approval in a prior approval supplement." **should be revised to read**:

[33] *Provided the test is not required by the CGMP for finished pharmaceuticals (***21 CFR 211***) to be conducted on each batch*, a proposal to drop a test, based on historical data, can also be submitted post approval in a prior approval supplement.

This reviewer concurs with the commenter's proposed revision, but suggests that a sponsor consider the PQIT alternative (with valid stages) or, if the test is not directly or indirectly required by **CGMP** and is truly superfluous, that test should not be filed in the application.

32 Page "58"

Lines "2120 – 2122," After the definition of "**Acceptance Criteria**: Numerical limits, ranges, or other suitable measures for acceptance of results of analytical procedures (ICH Q6A). In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production

batches have met certain criteria." **the draft should be revised to insert the definition of "Active Pharmaceutical Ingredient (API)" as follows:**

Active Pharmaceutical Ingredient (API): *The component containing the* ***drug substance*** *or* ***active ingredient*** *(***21 CFR 210.3(b)(7)***) that is available for inclusion into the formulation of a batch of drug product, or, the Agency's September 1996 definition,* **Active Pharmaceutical Ingredient (API):** "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug." (September 20, 1996, *Guidance for Industry Manufacture, Processing or Holding of Active Pharmaceutical Ingredients*, DISCUSSION DRAFT, pgs 2 - 3, at **D. 3**).

Although the commenter proposed two definitions, this reviewer thinks that the first is the definition that the Agency should add to the Glossary as follows:

Active Pharmaceutical Ingredient: The component containing the ***active ingredient*** (as defined in **21 CFR 210(3)(b)(7)** or ***drug substance*** (as defined in this guidance) that is available to the formulator for inclusion into the formulation of a batch of drug product.