Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
IV. A. Lines 246-250	The current text reads: "The submission can consist of the proposed comparability protocol in: A prior approval supplement that includes the proposed comparability protocol and test and study results as specified in the proposed comparability protocol and any other pertinent information to support a change covered under the protocol. The product already manufactured with the change can be distributed only after approval of the supplement."	As written, this is not a comparability protocol but a conventional PAS. Please differentiate to indicate the benefit of including the data and results as part of the PAS. We interpret this to mean that a wide scope PAS may also include a Comparability Protocol as one of its components or something else. Also, as written this may be interpreted to indicate that a Comparability Protocol should be submitted together with the data in the initial PAS from a proposed change which is contrary to the intent that the Comparability Protocol is optional. All that this reviewer and the commenters agree upon is that a "PAS may also include a Comparability Protocol as one of its components." This reviewer disagrees with the commenters' initial statement and note that it is at odds with the commenters' third statement. Finally, this reviewer leaves it up to the Agency to decipher and address the commenters' obtuse second and fourth remarks.
IV. A. Line 251 **Reference both sections III.B & IV.A.**	Information Request and Clarification	Please clarify whether the Comparability Protocol should be included in the Regional Quality Section of a CTD for a new NDA submission. Also, section IV.A. would be an appropriate section for FDA to address whether the submission of a Comparability Protocol in an original application will impact the review cycle. Finally, should revisions to the comparability protocol be tracked in the annual report, similar to the CMC?
IV. A. Lines 254 – 255	Change from: In all cases, a comparability protocol would be reviewed and approved by FDA prior to an applicant implementing a change under the protocol. Change to: In all cases, a comparability protocol would be reviewed and approved by FDA prior to the distribution of product manufactured using the changed process.	The concept here is not that product cannot be manufactured, for example, in full-scale plant trials or validation studies, but that drug sponsors may implement but not distribute until approval of the Comparability Protocol. This reviewer agrees with the commenters' on this point.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
IV. B. Lines 265-268	Change from: "The submission would include (1) the results of all tests and studies specified in your comparability protocol (2) discussions of any deviations that occurred during the tests or studies, (3) a summary of any investigations performed, and (4) any other pertinent information." Change to: "The submission should include (1) the results of all tests and studies specified in your comparability protocol (2) discussions of deviations, investigations, and (3) other information pertinent to the change being made." This reviewer cannot agree with the commenters' suggested changes here because to do so could be a subversion of the regulatory process. The Draft text here should remain as it is. --- The guidances should allow for interim steps/meetings /teleconferences (when a manufacturer gets data resulting from execution of the Comparability Protocol) before submitting a PAS. Discussion would include justification for why the data (although not exactly as expected from protocol execution) still supports the change. When there are instances where the sponsor conclusions regarding the data are different from FDA's, the differences may be resolved much more quickly in a discussion than by submitting a new PAS and waiting for the standard PDUFA timeframes. This reviewer disagrees with the commenters proposal that substitutes a "political" mechanism whereby a given "protocol failure" could be overlooked or ignored for the **CGMP** requisite more scientifically sound review process that the Draft proposes. The issue is not time; it is whether or not a firm adequately understands its own process. Whenever a CP fails to meet any of its pre-determined outcomes, it is or should be obvious that the sponsor's understanding of their systems and the product or products they produce is, at best, less than adequate. The sponsor needs to: **a)** improve their understanding of the interactions among the components, plans, processes, equipment, procedures, personnel, controls, in-process materials, products, and specifications and **b)** provide the data and information needed to support their "new" understanding. The PAS is needed to give the Agency the time it needs to review that information and data in the context of the failure and prior submission.	Delete items (2) and (3). GMP compliance information should not be included in the review supplement since not all investigations and deviations may be pertinent to the change being made. By definition, all investigations and deviations occurring during the study of the "changed" process are pertinent to that process. To introduce ambiguity in what should be submitted is, at best, anti-quality. It is and should be the responsibility of those Agency personnel to assess the pertinence and import of any and all aspects of the submission – not the sponsor. Contrary to the commenters' assertion, all review personnel including the Field Inspectorate have a duty to ensure that all manufacturing practices and the products they product are **CGMP** compliant. Obviously, it appears that the commenters wish to conceal certain facts from the reviewers and thereby ensure that the reviewers approve their submissions in support of process changes even when those process changes may not comply with **CGMP** and/or produce product that may not comply with **CGMP**. (Also, please define the term "deviations") "Deviations: actions or outcomes that diverge from those CGMP-compliant standards, actions or outcomes specified for the components, procedures, processes, in-process materials and products specified or addressed in the Comparability Protocol." For example, the presence of non-change-related, extraneous contaminants must be examined, but this is a GMP issue, not a registration issue. This reviewer disagrees, any non-change-related "deviation" and its investigation are CGMP-compliance registration issues that should be properly reported, investigated and discussed in a Comparability Protocol ← (Commenters' "Comments ..." and this reviewer's remarks continue in the adjacent column) ←

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
IV. B. Lines 276-282	Current statement: ~~"In certain instances, the tests and studies specified in an approved comparability protocol can lead to an unpredicted or unwanted outcome (e.g., test results do not meet predefined acceptance criteria).~~ If you decide to pursue the change, you should submit a prior approval supplement that provides the supporting data to justify why the change will not adversely affect the identity, strength, quality, purity, and potency of the specific drug product as these factors relate to the safety and effectiveness of the product." This reviewer notes that the commenters omitted the first sentence in the passage that they indicate they are commenting on. Add to the end: Where unexpected data are gathered, the change should be evaluated to confirm that the expected product is not compromised and that the results were inconsequential. As stated, the sentence seems to be devoid of any real substance. The **CGMP** regulations already require the investigation of any "unexpected" results vis-à-vis the product. Moreover, if valid, no result is inconsequential. Therefore, the commenters' first sentence contains should not be added. The results should be reported to the review division prior to formal submission of the data and, with the approval of the review division, may be submitted under the previously agreed submission requirements. This reviewer does not support adding this provision because it is at odds with establishing a uniform, fair review of all CPs on an equal basis and seeks to permit processes that are not comparable to be implemented as if they were comparable. Where the submission requirements of the product are not met, the submission should meet the filing requirements established in other related guidance, if applicable, or as determined in consultation with the review division. This reviewer cannot agree as, for CPs, this guidance supersedes prior guidances. There should be some allowance for discussion with the FDA reviewer to determine if the missed acceptance criteria is of so little consequence that the original reporting category is still appropriate and can be maintained. This guidance should make no such provision. Missing any **FDA**-approved acceptance criterion is of consequence.	If the studies in a Comparability Protocol lead to an unpredicted or unwanted outcome it appears that there are only 2 choices: not implementing the change and/or submitting a PAS. This reviewer agrees that the guidance ONLY permits the two choices the commenters have found to appear to be the case. However, modifications to the protocol to provide for a different change should be permitted. This reviewer cannot agree with this proposal because it attempts to convert a well-defined regulatory process into an undefined one. This is the case because the commenters propose no limitations to the "modifications" or to the "different change." Add a sentence to the end of the paragraph providing provision to allow for discussion if non-consequential acceptance criteria are not met. Since the approved acceptance criteria are the sponsor's criteria and are supposed to be based on the documented evidence of what is comparable product, an approved CP does not contain any such "non-consequential acceptance criteria" unless the commenters' position is that if any criterion is not met it magically becomes "non-consequential. Provisions should be made that if the acceptance criteria are not met, that should not automatically bump the implemented change to a PAS. Provisions have been made. The sponsor has two choices. The flexibility allowed in the Draft should be kept as it is because introducing more flexibility is not warranted. If the outcomes are not as the sponsor projects, it is or should be obvious that the sponsor does not truly understand the process and/or the existing process controls are, at best, marginal. Also, where the Comparability Protocol criteria are not met, we recommend the use of the reporting category that would normally apply for the type of change instead of being required to submit a PAS. For the same reasons as stated in this reviewer's response to the commenters' previous statement, this should be rejected. ← (Commenters' "Comments ..." and this reviewer's remarks continue in the adjacent column) ←

IV. D. Lines 284 - 296	General comment This reviewer finds that the commenters' remarks have little to do with what is stated in the text of the Draft. Moreover, this reviewer finds that the commenters are proverbially "*looking a gift horse in the mouth*" by failing to see that it provides the industry with a clear path to seek the modification of an approved CP prior to the completion of its execution when their studies, regulatory changes, or new science renders an approved protocol either non-**CGMP**-compliant or not scientifically sound. The text addresses factors that could "obsolete" an ***approved*** CP not the technology The text clearly indicates that the onus is on the firm that has the approved CP. As with all **CGMP**-compliance issues, the **FDA** has the oversight responsibility and authority stated To clarify the text, this reviewer would recommend modifying the text as shown in the adjacent column. → → → Recast in the manner shown, the commenters' concerns about the word "obsolete" are or should be "obsolete."	With regard to the determination of "obsolete", will investigators check for the "obsoleteness" of these protocols during inspections? Will FDA have any way of tracking these to determine when they become obsolete - or is it strictly up to the sponsor? FDA and sponsors can view the definition of "obsolete" (based on the considerations given here) differently. The determination that a technology is no longer adequate should lie with the firm, not with the Agency. We encourage the FDA to reconsider the practice of allowing a single individual or small component of the organization to determine that a modification is "obsolete" and, consequently, of reduced value. We encourage the Agency to evaluate only the adequacy of the change made and not the technology used to implement a change, where the change is "feasible and valuable" to the manufacturer and not necessarily at the pinnacle of technology. ← (This reviewer's remarks are presented in the next column) ← "New regulatory requirements, identification of a safety issue (e.g., screening for new infectious agents in materials from a biological source), identification of a new scientific issue, or technological advancement after the comparability protocol has been approved can render a protocol obsolete. We recommend you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the approved application and current FDA policy. We recommend you determine whether the tests, studies, analytical procedures, and acceptance criteria described in your approved comparability protocol are still appropriate prior to implementing and submitting a change under the protocol. If you find the approved comparability protocol is no longer correct or adequate, the current approved protocol should be modified or withdrawn. You should apply similar considerations to your submitted but, as yet, unapproved comparability protocols. [**Note:** The Agency can request additional information to support a change that is implemented using an ~~obsolete~~ approved protocol that the Agency subsequently finds to be obsolete because it is "out of date" with respect to **CGMP**, current Agency policy, and/or the firm's current pending or approved application or license, or its current pending or accepted DMF/VMF.]"
IV. E. Lines 302- 303		Please clarify whether notification of editorial changes to a comparability protocol in an annual report will be voluntary. Since guidance is <u>always</u> optional, this reviewer sees no need to explicitly state, "Voluntary actions are voluntary!" Hopefully, the Agency and these commenters will agree.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
Lines 320 A new sub-section is proposed	**A new sub-section is proposed** G. Can Comparability Protocols be Used with Combination Products?	Please include a section that addresses combination products and the applicability of comparability protocols. When a change is made to a component of a combination product under a Comparability Protocol, should the Comparability Protocol also include a section on how it affects the combined product? Provided the Agency agrees with this need and the text proposed is **CGMP** compliant, this reviewer would support the suggestions that the commenters have made here.
V. **Line 323**	Change from: "We recommend that a comparability protocol be developed and used within the context of existing change control procedures." Change to: "We recommend that a comparability protocol be developed and used within the context of existing change control procedures at the firm." This reviewer has problems both with the Draft's text and the commenters' proposed addition. To address both, this reviewer recommends the following: "We recommend that a comparability protocol be developed and used within the context of the existing **CGMP** change-control ~~procedures~~ requirements and the **CGMP**-compliant procedures that the sponsors have implemented."	Clarification. The reviewer agrees that the text needs clarification. Further, this reviewer agrees with the commenters' placing of the control procedures within the responsibility sphere of the filing firm (sponsor). However, the guidance needs to ensure that the sponsors not only have such procedures but that the procedures they have are **CGMP** compliant. This reviewer's alternative addresses both issues.
V. **Lines 325-328**	General Comment	Allow for writing Comparability Protocols as technology specific, across several products, which will result in time saving not only for industry but also for the FDA reviewers. This reviewer cannot agree with the blanket assertions made concerning the saving of time. For example, were the preceding to be allowed, a failure in one case would require the Agency to reject all and require a PAS be initiated for all. This is the case because all are in the one CP. How would this save time? Moreover, the difficulty with "technology" is that, while the technology may be the same for all products, the effects and outcomes may be radically different. For both of the preceding reasons, this reviewer opposes the commenters' suggestions.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. A. 1. Line 373	Add to the sentence ending in line 373: "Generally, data submitted as part of post implementation commitments may be provided to the FDA as a component of the Annual Report for the product." This reviewer sees a need for some type of statement along this line to be included in the text. However, the commenters' statement needs qualification and should be placed at the end of the section. Therefore, this reviewer would recommend the following be added after **Line 380** in the Draft, "Generally, post-implementation, commitment-related data, beyond that required to be submitted as a part of the change implementation notification submission, ~~should be submitted as part of post implementation commitments~~ may be provided to the FDA as a component of the Annual Report for the product."	Not all data will be collected at the time that information is provided in the follow-up submission, e.g., real-time stability data. This reviewer agrees with the commenters' statement about the "real-time stability data." There are two types of post-approval commitment-related data: A. Data that the supports the initial comparability of the "changed process" product and related data requested by the Agency that needs to be submitted with the "change" notification submission and B. Data, like stability data, that will, of necessity, have to be submitted at later times. Based on the preceding, this reviewer proposes the changed wording provided or better language be added at the end of this section.
V. A. 3. Line 397-398	Change from: "Validation of new modified analytical procedures or revalidation of existing analytical procedures should be performed, as appropriate. Change to: "Modified analytical procedures should be validated, as appropriate for their intended use Validation data should be retained at the manufacturing site for all methods." This reviewer does not agree with the commenters' proposed changes. However, this reviewer suggests that the Draft text should be changed to: "~~Validation~~ The initial validation of new modified analytical procedures or ~~revalidation~~ the on-going validation or verification of existing analytical procedures should be performed, as appropriate." The preceding modification matches the **CGMP** view that validation is a journey and not a destination.	Generally, only limited analytical procedure information is provided in the NDA for raw materials, starting materials, drug substance intermediates, excipients, and packaging materials. This section should not require more extensive information to support a change than what is required for a new drug. Analytical procedures are validated as appropriate for their use. This information should be held and be available at the manufacturing site. Apparently, the commenters have elected to ignore the draft guidance, "CMC Information: Availability," issued at about the same time as this Draft, which does require the same for the CMC section of all NDAs, and ANDAs, as well as DMFs/VMFs that address drug substance, drug products and drug components submitted under the DMF/VMF process. Since the commenters agree that this information must be acquired and be maintained (should be held and be available at the manufacturing site), then it should be provided to the Agency for inspection in the manner that the Agency asks.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. A. 3. Line 398 - 401	Change from: "The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA." Change to: "The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided (i.e., in AR or CBE) when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA." This reviewer cannot support the commenters' proposed change because it does not clarify; it attempts to limit how the information will be provided. If any "clarifying change" is needed, then, this reviewer would suggest that the reviewer's alternative be considered. → → →	Clarification The unmodified sentence already tells the sponsor when to report the information, "when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA," so the addition of the clause suggested is a) misplaced, b) adds confusion, and c) improperly limits the "when" to report the data. For all of the preceding reasons, the commenters' suggestion should be ignored or, failing that their modification clause should be moved to the end of the sentence and changed to include all possibilities as follows: "The protocol~~w ould~~ should specify that any new or revised analytical procedures and the appropriate validation ~~or revalidation~~ and/or verification information would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA (i.e., reported in an AR, CBE-0, CBE-30, or PAS, as appropriate)."
V. A. 3. Line 426 - 436	The text reading: "If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the recommended reporting category for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE30), the change would be reported as recommended for the specification change. If the recommended reporting category for the specification change is the same or lower than the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided when a post approval CMC change implemented using the approved comparability protocol is reported to FDA. --- In fact, if a new impurity is generated, then the reporting category should be PAS and appropriate acute and short-term chronic toxicity studies should be conducted. The referenced guidance, "*Changes to an Approved NDA or ANDA*" provides the definitions for the reporting categories and establishes guidance that the sponsor can use to assess which is the correct category for a given proposed change.	The intent of this text is not understood. Please clarify lines (revision of a drug product or drug substance specification), which is very confusing. Based on this reviewer's reading of the text, the "intent of Lines 426-436" is to provide the submitter with a clear understanding of the impact on the reporting category when the sponsor's changes an existing specification. As the Draft indicates, specification changes and their potential impacts are key factors in a) determining the reporting status of the comparability report and b) assessing the data submitted in that report. In general, changes that improve quality (e.g., changing the limit for Impurity A from "not more than 0.2 %" to "not more than 0.1 %" or changing the minimum purity from "not less than 98.5 % by weight" to "not less than 98.7 % by weight") are supportive of lowering the reporting category. Conversely, changes that adversely impact the product (e.g., changing the allowed tablet weight range from "190 mg to 210 mg" to "from 185 to 210 mg" or adding a limit for a new impurity) are supportive of raising the reporting category. ← (This reviewer's remarks continue in the adjacent column) ←

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. B. 3. Lines 484 -486	Change from: "A comparability protocol would normally include a plan to compare the physical characteristics (e.g. polymorph forms, particle size distribution) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product." Change to: "A comparability protocol would normally include a plan to compare the physical characteristics (e.g. polymorph forms, particle size distribution) when (1) comparability is established after the final solution step of the drug substance synthesis and (2) these characteristics are relevant to the safety and/or efficacy of the drug product. This reviewer disagrees with the commenters' proposal. However, the reviewer would change the text slightly to reflect the other common physical properties that can be critical to the comparability of the drug substance used to produce comparable drug products: "A drug substance **comparability protocol would normally include a plan to compare the physical characteristics (e.g.,** for solids, **polymorph forms, particle size distribution,** bulk and tapped density, flow, permeability, intrinsic solubility; for liquids, viscosity, refractive index, color, density) **of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product.** Similarly, a drug product protocol would normally include a plan to compare the physical characteristics (e.g., for solids, hardness, friability; for semisolids, color, density; for suppositories, softening temperature, density; for suspensions, settling time, color, density; for liquids, viscosity, refractive index, color, density, particulates; for solid aerosols, particle size distribution, dose dispersion pattern; and for liquid aerosols, droplet size distribution, dose dispersion pattern) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product."	As per BAC PAC I, an examination of physical characteristics is required only when equivalence is demonstrated after the final solution step. This "Rationale" statement has no bearing on the Draft's text because the stated comparison is for the product that, in this context, is obviously the drug substance. The BACPAC I guidance is designed to restrict the comparison to the final products which the statement has already done. However,t he examples list is incomplete and should be expanded to ensure that other key physical properties of the drug substance are at least considered. Moreover, as written, the text only applies to a solid drug substance (a/k/a active ingredient or active pharmaceutical ingredient [API]). Given the preceding, the only apparent reason the commenters proposed the change was to remove the phrase "**of the product produced using the old and the new processes**" to permit the firms to propose comparisons of the product from the new process to other than the old process (for example, a comparison to some reference material) even though doing such is <u>not</u> in keeping with maintaining the post-change product's comparableness to the pre-change product. For all of the preceding reasons, the commenters' proposal should be rejected. Moreover, the text needs to be augmented to address the CPs for the drug product and its various common dosage forms.
V. B. 3. Lines 491-492	Change from: "The studies would assess product-related impurities and process-related impurities, including, if applicable in-process reagents and catalysts." Change to: "The studies would assess product-related impurities and process-related impurities, including, if applicable, in-process reagents, catalysts, **and solvents**."	As per BACPAC I, demonstration of equivalence includes assessing residual levels of existing and any new solvents.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. B. 3. Line 494	Add as next sentence on this line "Comparability of the impurity profile can be established by testing an appropriate isolated intermediate following the change or the drug substance." This reviewer does not agree with the commenters' proposed addition. However, this reviewer would support the following modified version of the preceding: "Comparability of the impurity profile can be established by testing the drug substance or the drug product, or, *provided a) no new impurities are found and b) the levels found for each of the existing impurities in the postchange process intermediate are not greater than the levels found in the same prechange process intermediate for a drug substance process*, an appropriate isolated intermediate following the change ~~or the drug substance~~."	It is necessary to confirm that the demonstration of comparability at a certain step will not require complete processing from the modified step through unmodified steps to drug substance. The commenters' wish to minimize the processing of the intermediate to the final drug product needs to be balanced against the reality that intermediates that contain new impurities or increased levels of existing impurities need to be processed further (through all of the purification steps in the process) to ensure that the resulting drug substances are comparable. This is the case because the carrying of new impurities or higher levels of the existing impurities into the post-change drug substance makes the post-change drug substance not comparable to the pre-change drug substance. In addition, the issue of impurities in the drug product should only be assessed at the end of the process that manufactures the finished drug product.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. B. 3. Lines 518 -520	Change from: "We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new production process, if appropriate." Change to: "We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be reassessed for the new production process, and revalidated, if appropriate." This reviewer disagrees with both the original text and the commenters' proposed revision. This reviewer proposes the following: "**We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be ~~revalidated~~ validated for the new production process~~, if appropriate~~** for both drug substances and drug products to at least the extent required by **CGMP** as set forth in the **21 CFR 211.110.**"	Validation may or may not be appropriate in all cases. Each case will require individual evaluation. Validation may or may not be appropriate in all cases. Each case will require individual evaluation. This reviewer disagrees. The **FDC Act** at **21 U.S.C. 351(a)(2)(b)** states that a drug is adulterated "**if it is a drug and 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.**" Though the regulations governing the drug substance have not been published, the Agency rightly applies the published drug regulations set forth in **21 CFR Parts 210 through 226** to both drug substances and drug products. **21 CFR Subpart F**—Production and Process Controls sets forth the regulations that govern process controls. In **Subpart F, 21 CFR 211.110,** "Sampling and testing of in-process materials and drug products," states (underlining emphasis added) at (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. ..." Therefore, a firm is required to evaluate each of their process controls in each iteration of the process in a manner that validates that control. Thus, the Agency should not propose, and the sponsors cannot do, less in this case. [**Note:** As the regulations so clearly indicate, validation is an ongoing journey and thus, though used, the term "revalidated" is inappropriate for what is an ongoing activity required for each iteration of the process as the applicable **CGMP** regulation so clearly does.]
V. E. Line 576	General comment on the section	FDA should discuss their expectations for use of a Comparability Protocol for the relocation of the same equipment to another already compliant, inspected, or approved area. This could be offered as a positive example of when a Comparability Protocol can decrease reporting burden. This reviewer would suggest that this commenters' recommendation be given careful consideration but, if added, the guidance should limit such to relocations on the same campus.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. E. Line 559-579	Add to the end of line 579: "If the submission of the prior approval Comparability Protocol supplement would require a site inspection, the applicant is responsible for insuring that the site has a satisfactory CGMP inspection for the type of operation prior to commercial distribution of a change in accordance with a commitment to the approved Comparability Protocol." This reviewer opposes the commenters' addition. It does not conform to the expectations of the **FDC Act** that the Agency only approve submissions for processes in facilities that **are CGMP** compliant (**21 U.S.C. 351(a)(2)(B)**). Since the preceding is the case, this reviewer would propose adding the following after **Line 579**, "Given the requirements of the **FDC Act**, the Agency cannot approve a Comparability Protocol ("CP") for a ***facility*** that does not have inspectional confirmation of satisfactory **CGMP** compliance. In cases where a new facility is proposed, the reviewer will, as with any other type of PAS, verify the proposed facility's **CGMP** compliance status. In cases where the proposed ***facility*** (not the site) does not have a history that supports satisfactory **CGMP** compliance, the CP reviewer will notify the Field Inspectorate and work with them to schedule the needed facility inspection. Firms should not submit a CP unless they know that the facility is ready for a "PAI" site audit on the day the CP is submitted. [**Note:** CPs that name facilities at which the Agency *subsequently* finds unsatisfactory **CGMP** compliance at the facility named should, if not approved, be rejected and, if approved, should have their approval revoked or suspended until the facility attains satisfactory **CGMP** compliance status.]"	We suggest that the Manufacturer should be able to work with the local FDA office to schedule inspections related to the implementation of the comparability protocol. The Guidance should more clearly state whether FDA will permit a supplement in a non-prior-approval reporting category for a change to a new site which has not been inspected or does not have a satisfactory CGMP inspection; since prior approval inspections are usually prompted by, or requested via, the PA supplement process. For instance, standard packaging site changes require CBE-30 supplements, unless the site does not have a satisfactory CGMP inspection. An approved Comparability Protocol could allow for a packaging site change to be reported in an annual report, along with a statement (Lines 570-573) that the move will be implemented only when the site has a satisfactory CGMP inspection for the type of operation. This Guidance, as written, does not provide for use of such a Comparability Protocol, which imposes the responsibility of insuring completion of a satisfactory CGMP inspection without a PA supplement. The **FDC Act** is quite clear with respect to requiring **CGMP** as a precondition for the manufacture of a drug. In 1988, the US Supreme Court ruled that the FDA administrators have no latitude with respect to clearly written statute or regulation that governs the pharmaceutical industry. Both the law and the regulation (**21 CFR 210**) both make **CGMP** compliance a prerequisite for the commencement of manufacture Legally, the Agency can do no less. Thus, the Agency should not approve any submission that the Agency knows does not meet all of the prerequisite **CGMP** minimums set forth in the **FDC Act** and the implementing **CGMP** regulations.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. F. Lines 581-586	Add to the ends of lines II.B., (L 114) and V.F. (L 586): Comparability Protocols are not to provide a list of supporting data that the applicant will provide to support changes that current guidance classifies as annual reportable. This information must accompany the change when it is reported in the Annual Report Section This reviewer cannot agree with the proposed insertion because (1) the submission of a CP is an option and (2) if the sponsor elects to pursue this option, CPs have the same internal reporting requirements as a PAS because the Agency classifies them as a PAS. Moreover, the commenters' rationale seems to be derived from unpublished guidance discussions that have no currency. Therefore, the commenters' proposal should be rejected. This alternative choice was included because it seemed to this reviewer that the section and context logically pointed to an alternative that the commenters somehow missed.	Prior to the 11/99 PAC Guidance, applicants included a form of Comparability Protocol or interchangeability protocol which described changes that appeared to reduce the reporting category from CBE to AR (based on 2 1 CFR 314.70 requirements. In alignment with the allowable changes in the 11/99 PAC Guidance, there is no need to describe minor, annual reportable changes in a Comparability Protocol, except to provide a list of supporting data that the applicant will provide. FDA should state that they do not expect to see Comparability Protocols for Container/Closure changes that are described as annual reportable in the 11/99 PAC Guidance to simply provide a list of supporting data. **Note:** As far as this reviewer was able to ascertain, there is no official packaging PAC (11/99 PAC) guidance that the FDA has published as the commenters seem to indicate and the search of the entire FDA site for "11/99 PAC Guidance" found no matches. This reviewer did find evidence that such "PACPAC" guidance was "discussed" and "planned" but nothing more. On this basis alone, the commenters' proposal should be dismissed as wishful thinking on their part. Please clarify the use of the word "repetitive" in line 585. Does this mean • a single change applied to numerous applications or • a series of changes that have predefined acceptance criteria but which may extend beyond any single change? • Or does it, *as the context indicates*, simply mean a single change, like a bottle source or a packaging site change, that applies to several different packaging formats for the same drug product? This reviewer leaves it up to the Agency to respond as it sees fit.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. H. Lines 599-602	Change from: The protocol would include a commitment to provide a letter authorizing the FDA to review the master file when a post-approval CMC change implemented using the approved comparability protocol is reported to the FDA. Change to: The DMF holder should confirm that changes are properly reported to the FDA. Additional updates may be PA supplement provided at any time or during the annual update. This information should include updated reference citations in the DMF. The DMF holder may unilaterally expand the information supporting the NDA holder by inclusion of additional reference information in the update. This reviewer cannot agree with the change proposed because the commenters who proposed it are obviously unaware of the trade secret provisions appertaining to DMFs/VMFs that prohibit the **FDA** from monitoring their content. Its contents are "trade secrets" and not available for review without an authorizing letter from the DMF/VMF holder or, if the DMF/VMF holder is located on foreign soil, the DMF/VMF holder's legally empowered representative (agent). The **FDA** only tracks the required annual DMF/VMF update and simply files that and all other DMF/VMF filings. *Unlike the drug product AR*, A DMF/VMF filing is not automatically reviewed nor is it automatically reviewable.	The Guideline for Drug Master Files (September 1989) does not indicate that a new authorization letter is required whenever a change is made to a specific DMF. However, this section appears to require a new Letter of Authorization if there is an NDA change which may reference a different master file or, perhaps a different portion of a master file. This section, as written, implies that the NDA holder has intimate knowledge about the content of the master file and must understand that the initial authorization did not grant access to existing sections of a master file. A new letter is needed because in support of the CP, the DMF holder will have added new information to the DMF that the **FDA** needs a new letter to permit it to review the new information in the file. Moreover, the control of the quality attributes of a DMF-controlled drug substance, other component or container closure system is a contractual matter between the DMF holder and the drug product manufacturer. The **CGMP** regulations place the burden on the manufacturer to only accept incoming items that are the "same" as those that the manufacturer used to obtain Agency approval or license. Therefore it behooves the drug product manufacture to have clear contractual provisions that ensure that the manufacturer is kept informed of all changes made by the DMF holder. This the case because, while the DMF holder may be filing them annually, the Agency cannot, except in the inspection process (PAI, biannual or for cause) review the changes being made unless the DMF holder provides a letter authorizing the Agency to do so. [**Note:** In light of this reality, perhaps the industry should be lobbying for biannual, or more frequent, inspections for all DMF holders.] Moreover, if the Agency finds a problem with the drug product that comes from a change in the chemical or physical properties of the drug substance, the Agency holds the drug-product manufacturer most accountable because they are supposed to make certain that components that are different (from those components originally used to obtain Agency acceptance, approval, or licensing) are not used to make drug product. The DMF holder's responsibility in such cases is clearly secondary.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. H. Lines 599-602 (Continued)		Comments regarding text (Continued) Many master file holders are very reluctant to provide details about their master files that would allow for or facilitate clean, clear references. Please clarify why the FDA needs a copy of the DMF authorization letter from the DMF holder when the regulatory file is reviewed for a change contained in a DMF (e.g. container resin change). We believe that a new DMF authorization letter is unnecessary since the FDA must have received the DMF letter at the time of original review of the regulatory file. The prior letter only authorizes a "one time" review of the file for the sole purpose of "initial acceptance" that the file supports a **CGMP** compliant material component, container closure component, or other material. It does not authorize future reviews of future information. Therefore, each time a DMF/VMF-controlled process is changed and the change has a material effect on the drug substance, other component, or container closure system, the affected drug product firm needs to obtain and submit a letter authorizing the FDA to review the appropriate sections of the DMF/VMF. As MFs are not "approved" documents, how is the Comparability Protocol to be approved when submitted to a MF? How is notification of "acceptance" of the Comparability Protocol received from the FDA? As the next Draft paragraph indicates, that is a question for the FDA whose exact answer has not yet been formulated. Under its existing policy, the Agency would simply "accept" a CP filed for a DMF/VMF holder when (during the next inspection) the Agency finds it acceptable or reject it when it is not. If the NDA/ANDA/NADA/ANADA holder submits a filing referencing that same DMF/VMF process and product, the filing would be either approved or rejected. In Case 1, only the DMF/VMF holder would be notified; in Case 2, both holders would be notified (the DMF/VMF holder by an acceptance letter and the other by an approval letter). In Case 2, a DMF holder letter would be needed authorizing the Agency to **a)** review the appropriate files to determine if the proposed process change and post-change product would be "acceptable" if the acceptance criteria proposed are met and **b)**, when the studies have been completed, again review the files for authorization to ship the post-change product

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. H.	General Comment	A review period for veterinary Comparability Protocols should be defined. Veterinary drugs are currently outside the scope of PDUFA and CVM offers no review period. This reviewer agrees and recommends adoption of the periods established for human drugs
V. H. Line 612	The text notes that Comparability Protocols are "product specific". Change to: Comparability Protocols are specific for changes that may apply to a single product or multiple products where the same change is made.	The Comparability Protocol may become a significant component in multi-product manufacturing facilities. In such cases a simple cross-reference between files should be adequate and the Comparability Protocol would not be product specific.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
V. H. Lines 610-617	Recommended Language: The provisions for submitting a comparability protocol in a master tile will be the subject of future revisions to CDER's Guideline for Drug Master Files and CVM's Guidance for Industry for the Preparation and Submission of Veterinary Master Files. Until those revisions have been made, comparability protocols for master files are not included within the context of this Guidance. This reviewer does not agree with the commenters' proposal. Comparability protocols are a valuable tool that the DMF/VMF holder can, if followed, use to: 1. Provide themselves with the assurance the holder needs to have that, as "comparable" is defined by the FDA, the changes they implement do produce postchange product that is comparable chemically and physically to the FDA "accepted" product, 2. Ensure that the holder will have no change-related inspectional issues in their next general CGMP inspection, and 3. Ensure that their customers continue to receive drug product that is comparable to the prechange product the FDA "accepted" so that customers have little or no risk of making unacceptable drug product when they attempt to use postchange product in their approved drug-product processes. In this reviewer's experience, there have been several cases where an innocuous change by a DMF holder has resulted in post-change API lots that their customer could not convert into acceptable drug product using the drug-product manufacturer's approved process. In every case, part of the "root cause" solution was to improve the working and contractual relationship between the parties and, at a slight increase in component cost, appropriately tighten the incoming contractual acceptance criteria that both parties agreed should be met.	We are uncertain of the benefit that a DMF holder will gain by providing a Comparability Protocol, since they have no regulatory "Prior Approval" issues with which to contend. The commenters are correct. However, DMF/VMF holders do have **CGMP** compliance and customer issues that should compel them to only make changes that do not change the nature of their product in any material way. Since the Agency's method of auditing for their **CGMP** compliance is, of necessity, inspection, the DMF/VMF holder and the Agency both have much more at stake in an inspection than non-DMF/VMF holders do. In general, the finding of non-comparability in an inspection, should immediately suspend the holder's "acceptance." For holders located on US territory, the Agency can, should and has, simply had a local health official or, in some cases, federal marshals, padlock the facility and issue seizure orders for lots in commerce. For foreign holders, the Agency need only issue an Import Alert to customs and initiate seizure actions for any bulk component in commerce. Do you intend this to say that the NDA holder can reference the comparability protocol in the DMF and be required to do no additional work? The text does not state what the commenters' remarks state; moreover, nothing could be further from the truth. What is intended is to notify the drug product manufacturer to have a strong contractual and working agreement with their DMF/VMF holder suppliers and work with them to ensure that the changes the component manufacturer makes do not adversely impact their drug product. This could be one of the Agency's not so subtle ways of reminding the drug product manufacturer that they, not the Agency, bear the responsibility and accountability for the risks they elect to take. Ifa DMF/VMF holder will not, for a fair price, agree to provide the information needed by the drug product manufacturer and work with that firm to address change issues, the drug product manufacturer should simply not buy that component from that source.

Aventis Pharmaceutucals, Inc.'s Submission, Dated June 23, 2003, To Docket 03D-0061: "C-05"

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

These commenters begin by stating, "Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled 'Comparability Protocols - Chemistry, Manufacturing, and Controls Information'. This draft guidance provides recommendations to applicants on preparing and using comparability protocols for post-approval changes in chemistry, manufacturing and controls (CMC) information. We offer the following comments and questions for your consideration."

"Section II. BACKGROUND
Page 2, Lines 39-45

As an applicant, you are responsible for assessing, prior to distribution of a product, the effect of any postapproval CMC changes on the identity, strength, quality, purity, and potency of the product as these factors relate to the safety or efficacy of the product (section 506A(b) of the Federal Food, Drug and Cosmetic Act (the act)). Such an assessment often includes demonstration that the pre- and postchange products (i.e., products manufactured prior to and subsequent to a change are equivalent. Postapproval CMC changes must be reported to FDA in one of four reporting categories (Section 506A of the Act):

We suggest adding a Glossary to either this BACKGROUND section or the INTRODUCTION section to provide the sponsor with a clear definition of regulatory and technical terms used in preparing a comparability protocol.

Examples of terms to be included in the suggested Glossary are as follows:

Comparable
Drug
Comparability protocol
Comparability report
Analytical reference standard (e.g., ***USP Reference Standard***, ***NIST Reference Standard***)
Recognized consensus standard (e.g., ***ANSI Z 1.4***, ***ANSI Z 1.9***, ***ISO 3951***)
Related CMC ~~changes~~ change
Unrelated CMC ~~changes~~ change
Drug substance
Intermediate
Drug product
~~Isoforms~~ Isoform
Orthogonal Testing
~~Product-specific~~
~~Process-specific~~
Current protocol
Obsolete protocol ~~(criteria)~~
~~Qualification or validation lots~~ Validation or verification lot
PAS
CBE-30

CBE-0
AR
Reportable categories
FDA review period for comparability protocol
Method validation
Process validation
~~Criteria for non-comparability~~
Stability-indicating ~~assays~~ assay"
Representative sample
Descriptive statistics
Population statistics
Statistical quality control (SQC)
Minimum process capability
Batch
Lot
Factor (n.)
Attribute
Characteristic (n.)
Variable (n.)"

In general, this reviewer agrees that the definition of terms is important in any guidance document and supports the commenters' inclusion of most of the terms in their list.

However, this reviewer notes that the critical term "Comparable" that should be included and would propose that that term ands its definition be included as follows:

"**Comparable:** For the purposes of this guidance, alternative processes and products produced by alternative processes are deemed comparable to the original **FDA**-accepted process if and only if the alternatives and their products have been shown to meet all their existing safety parameters, and identity, strength, quality, and purity specifications as well as all of the applicable **CGMP** requirements that appertain thereto."

Then, the definition of derived terms such a "Non-comparable" ("not comparable") and "Criteria for non-comparability" are obvious and do not need to be included in the "Glossary."

In cases where the definitions suggested by the commenters are in the Federal Food, Drug, and Cosmetic Act as amended ("**FDC Act**," **21 U.S.C. Title** 9) in **21 U.S.C. Chapters 321** and **321b,** the current good manufacturing practice ("**CGMP**") regulations for drugs and drug products (**21 CFR Chapters 210** through **226**) in **21 CFR Section 210.3**, and in the submission filing regulations, the definitions in said regulations should be used.

In cases where those definitions are contained in other related guidances or draft guidances, those definitions should be appropriately included.

In general,d erived and plural terms should not be defined.

Based on the preceding, the terms that need not be defined have been stricken from the list and certain other key terms have been suggested.

However, this reviewer would leave it up to the Agency to decide which of the listed terms need to have their definitions included in this guidance.

"Section II. BACKGROUND
Page 3, Lines 81-91

This guidance describes the general principles and procedures associated with developing and submitting a comparability protocol to the FDA. The guidance also describes the basic elements of a comparability protocol and specific issues to consider when developing comparability protocols for changes in:

- *the manufacturing process*
- *analytical procedures*[4]
- *manufacturing equipment*
- *manufacturing facilities*
- *container closure systems*
- *process analytical technology (PAT)"*

We suggest adding *starting materials* and *raw materials* to the list of basic elements as these are critical CMC elements, which are subject to change during both drug development and post approval."

This reviewer suggests that the proper phrase to add would be "*components* (also known as *starting materials* and *raw materials*)."

This is the case because the term "component" is the term used in **21 U.S.C. 321(g)(1)** in the **FDA Act**'s definition of "drug" and defined in **21 CFR 210(b)(3)**.

Further, this reviewer would recommend using the term component as much as possible and minimizing the use of the phrases "*starting materials*" and "*raw materials*" in this and other guidances.

"Section II. BACKGROUND
Part A. What is a Comparability Protocol?
Page 3, Lines 97-103

A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is optional.

We suggest that this guidance not be restricted to just a comparison of drug products as there are examples of change controls that focus directly on drug substance.
Comparability of drug products may not need justification if drug substance CMC changes have no adverse effect on the safety or efficacy of drug product attributes. The CMC distinction between drug substance and drug product changes is also consistent with the current CTD format. However, if CMC changes occur in a drug substance process that affect the drug product's attributes then drug product comparability is justified."

While this reviewer agrees with the commenters that comparability protocol guidance need not be restricted to drug products, this reviewer, *recognizing the difficulties in doing so that arise from the DMF/VMF status of most drug substances*, leaves it up to the Agency to decide whether to make the suggested revision.

However, this reviewer notes that the only way that the only way a drug product manufacturer can demonstrate that a drug substance change has "no adverse effect on the safety or efficacy of drug product attributes" is for the manufacturer to manufacture batches in which the changed drug substance is used, and perform intensified assessments on

said batches and determine that, compared to the data and results from the intensified testing performed on the batches used obtain Agency approval or licensing, the post-change batches are comparable to the pre-change "approval" or "licensing" batches.

Additionally, this reviewer would suggest making the grammatical change suggested previously by correcting the phrase, "**for assessing the effect of specific CMC changes ~~in~~ on the identity, strength, quality, purity, and potency of a specific drug product**" as shown.

Finally, as this reviewer has previously suggested, he recommends changing the text to read:

"**A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes ~~in~~** on **the identity, strength, quality, purity, and potency of a specific ~~drug~~ product** (in-process material, intermediate, drug substance or drug product) **as these factors relate to the safety and effectiveness of the** final **product.**"

"Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part A. How Does a Comparability Protocol Affect the Reporting of CMC Changes?
Page 5, Lines 146-157

A comparability protocol prospectively specifies the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be achieved to assess the effect of CMC changes. A well-planned protocol provides sufficient information for FDA to determine whether the potential for an adverse effect on the product can be adequately evaluated. With comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be implemented without an approved comparability protocol. Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g., from PAS to CBE-30, CBE, or AR). In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR).

It is unclear what the Agency means by the following sentence:

'With comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be implemented without an approved comparability protocol.

Does this mean that the Agency can set a lower reporting category for the same change(s) if the same change(s) were submitted without an approved comparability protocol? We suggest including additional text to this section for clarification."

This reviewer agrees with the commenters' remarks and suggests that the changes proposed in the previous commenters' remarks be considered.

"Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part B. When Might a Comparability Protocol Be Useful for a CMC Change?
Page 5, Lines 162-163

In addition, a comparability protocol can describe single CMC change or multiple related changes. We suggest adding text to this section that clarifies the meaning of 'multiple related changes'."

This reviewer agrees with the commenters' remarks and suggests that the changes proposed in the previous commenters' remarks be considered.

"Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL

Part B. When Might a Comparability Protocol Be Useful for a CMC Change?
Page 5, Lines 163-171

However, we recommend that each change be discrete and specific. A comparability protocol can be particularly useful for changes of a repetitive nature. We recommend that you have sufficient manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and acceptance criteria appropriate for demonstrating that the CMC change or changes will not adversely affect the product. We recommend that comparability protocols be considered for CMC changes that applicants anticipate will be made.

It is unclear what the Agency means by 'sufficient manufacturing information'. We suggest adding text to this section for clarification."

This reviewer agrees with the commenters' remarks and suggests that the changes proposed in the previous commenters' remarks be considered.

"What range of stability data would FDA recommend at the time of submitting the comparability report?"

This reviewer would recommend, as he has previously, that the Comparability Protocol report should contain the stability reports and data from not less than three month of accelerated testing and the three-month's long-term stability test for all of the standard test stations including, where appropriate, stations for product container orientation.

"Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part B. When Might a Comparability Protocol Be Useful for a CMC Change?
Page 5-6, Lines 173-188

We recommend you consider product-specific and process-specific ~~attributes~~ factors or characteristics *when determining whether to develop a comparability protocol. ~~Attributes~~* Characteristics or variable factors *can include, but are not limited to the following:*

- Complexity of the product structure
- Ability to characterize the chemical, physical, microbiological, and biological properties of the product
- Degree to which differences in product structure and physical properties (e.g., polymorph) can be detected
- Degree of product heterogeneity if present
- The effect on safety of changes in the impurities
- The robustness of the product (i.e., the availability of product to remain unaffected by changes)
- Rigorousness of the manufacturing process controls (i.e., the availability of the manufacturing process controls to ensure that the product remains unaffected by changes)"

With the replacement of the word "*attributes*" with the phrase "characteristics of variables factors" to align the terminology usage with the scientific connotations of the words in question, this reviewer finds the Draft's text is acceptable

"For clarity, we suggest including text that distinguishes between examples of product-specific and process-specific ~~attributes~~ characteristics or variable factors."

This reviewer agrees with the commenters' remarks and suggests that illustrative examples like those proposed in the previous commenters' remarks would a good way to address the concerns of these commenters.

"Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part A. How Should a Comparability Protocol be Submitted?
Page 7, Lines 238-252

You can submit a comparability protocol in a prior approval supplement or as part of the original application. We recommend that you indicate clearly in the cover letter that you are submitting a comparability protocol.
The submission can consist of the proposed comparability protocol in

- *A prior approval supplement that is reviewed and approved prior to generating data supporting the change*
- *A prior approval supplement that includes the proposed comparability protocol and test and study results as specified in the proposed comparability protocol and any other pertinent information to support a change covered under the protocol. The product already manufactured with the change can be distributed only after approval of the supplement.*
- *An original application that is reviewed and approved prior to generating data supporting the change"*

"Where are the comparability protocol and report placed within the structure of the CTD?

Would comparability protocols be placed as regional-specific templates in the specific sections under which they directly apply, (i.e., If a comparability protocol is for a drug product manufacturing change, would the template be placed under CTD Section 3.2.P.3.3 - Description of the Manufacturing Process?

If so, what would be recommended for comparability protocols that support multiple changes?"

This reviewer can only recommend that the Agency should answer these commenters' questions.

"Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part A. How Should a Comparability Protocol be Submitted?
Page 7, Lines 254-255

In all cases, a comparability protocol would be reviewed and approved by FDA prior to an applicant implementing a change under the protocol.

The guidance states that a comparability protocol must be approved prior to implementing the change."

This reviewer notes that including this "review and approval before implementation" text is problematic on several grounds (see previous commenters' applicable remarks) and is one of the reasons that extending the proposed Draft to drug substances would be difficult because most firms consider the processes for such to be "trade secrets" that are not, in general, reviewed or reviewable when they are filed under the DMF/VMF procedures.

Though such drugs are covered by the biannual and "for cause" inspection process, their filings are currently not reviewable unless the DMF/VMF holder grants the Agency the right to review them and, in general, a drug product manufacturer references the drug substance in a filing that directly or indirectly an Agency requirement for review.

"Since protocol review times are not defined or described in this guidance, will a comparability protocol be reviewed within the same 45 day review period that is defined by the Guidance for Industry: Special Protocol Assessment (May 2002)?

Will FDA designate a fee structure for the review and approval of a comparability protocol once a predetermined review period is set?"

"Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part D. When Does a Comparability Protocol Become Obsolete?
Page 8, Lines 286-291

New regulatory requirements, identification of a safety issue (e.g., screening for new infectious agents in materials from a biological source), identification of a new scientific issue, or technological advancement after the comparability protocol has been approved can render a protocol obsolete. We recommend you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the approved application and current FDA policy.

Currently, there are no compendial test methods available to quantitatively assess BSE/TSE risks. Screening tests for new infectious agents from biologically-sourced materials are in a dynamic state. Changes occur constantly as new proven technologies and methods are acquired."

This reviewer agrees with the commenters' remarks, but does not understand the need to express them here except as a lead in to their question.

"Would the CMC information required obtaining an EU Certificate of Suitability be acceptable to FDA, or would FDA require additional/different CMC information for BSE/TSE safety assessments?"

"Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part D. When Does a Comparability Protocol Become Obsolete?
Page 8, Lines 294-296

If you find the comparability protocol is no longer correct or adequate, the current protocol should be modified or withdrawn. FDA can request additional information to support a change that is implemented using an obsolete protocol.

The guidance states that FDA can request additional information if an "obsolete" protocol is used. We suggest that text be added to this section that clarifies the criteria for defining an "obsolete" protocol."

This reviewer disagrees with the commenters' suggestion.

However, as reflected in the prior sections where the commenters raised similar issues regarding "obsolete" protocols, this reviewer again recommends changing the text in the Draft (**Lines 286** through **296**) to read as follows:

"New regulatory requirements, identification of a safety issue (e.g., screening for new infectious agents in materials from a biological source), identification of a new scientific issue, or technological advancement after the comparability protocol has been approved can render a protocol obsolete. We recommend you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the approved application and current FDA policy. We recommend you determine whether the tests, studies, analytical procedures, and acceptance criteria described in your approved comparability protocol are still appropriate prior to implementing and submitting a change under the protocol. If you find the approved comparability protocol is no longer correct or adequate, the current approved protocol should be modified or withdrawn. You should apply similar considerations to your submitted but, as yet, unapproved comparability protocols. [**Note:** FDA can request additional information to support a change that is implemented using an ~~obsolete~~ approved protocol that the Agency subsequently finds to be obsolete because it is "out of date" with respect to **CGMP**, current Agency policy, and/or the

firm's current pending or approved application or license, or its current pending or accepted DMF/VMF.]"

"Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part B. Does FDA Have Specific Concerns About Changes in the Manufacturing Process That Should Be Addressed in a Comparability Protocol?
Page 13, Lines 495-498

The predefined criteria would indicate when qualification studies will be warranted to evaluate an increased level of an existing impurity or a new impurity (or an applicant could reference a relevant FDA guidance that recommends qualification levels).

Does reference to a 'relevant FDA guidance' exclude ICH Q7A?"

Though this reviewer cannot answer for the Agency, this reviewer notes that the **FDA** should only reference guidances that it has issued.

Thus, if the **FDA** finds a given ICH or, for that matter, ***USP*** document to be the same as the Agency's current thinking on a subject, the **FDA** should publish its own version of that guidance and reference it.

The **FDA**, bound by the **FDC Act** and the statutes of the United States should only reference documents that are either "recognized American standards or their ISO equivalent" or ones they issue.

This is the case because other agencies, not governed by the **FDA,** can change their guidance documents in ways that renders them at odds with the **FDC Act**, the **CGMP** regulations, and/or **FDA**'s current thinking.

The ICH is a consortium of three (3) pharmacopeial organizations whose actions are not controlled by the **FDA**.

As such, the **FDA** should not directly reference ICH guidances.

"When does FDA expect to harmonize US Guidances with ICH documents?"

Again, this reviewer cannot answer for the Agency.

However, to the extent that the **FDA** is bound by the **FDC Act** and the **CGMP** regulations and the ICH is not, the Agency cannot "harmonize" some of the guidances until and unless the other member states adopt a **CGMP**-compliance, "**CGMP** minimums" approach to their quality systems.

Since the "national" drug quality system of one of the ICH members, the EU (or EC), is not a "compliance minimums" approach to guaranteeing quality, harmonization oft he systems may not be possible.

This difference has even been formalized in the definitions set forth in **21 CFR 26.1(c)** which states. "Good Manufacturing Practices (GMP's). [The United States has clarified its interpretation that under the MRA, paragraph (c)(1) of this section has to be understood as the U.S. definition and paragraph (c)(2) as the EC definition.]

(1) GMP's mean the requirements found in the legislations, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing, packing, and/or holding of a drug to assure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess.

(2) GMP's are that part of quality assurance which ensures that products are consistently produced and controlled to quality standards. For the purpose of this subpart, GMP's include, therefore, the system whereby the manufacturer receives the specifications of the product and/or process from the marketing authorization/product authorization or license holder or applicant and ensures the product is made in compliance with its specifications (qualified person certification in the EC).

Further the current "Common Technical Document" (CTD) draft also explicitly recognizes that there are areas that cannot be harmonized and appropriately provides sections for incorporating such.

Indeed, in their prior remarks concerning the placement of a Comparability Protocol in a CMC submission, the commenters recognized that reality.

Finally, given its limited resources, the priority of the Agency should be to issue **CGMP** guidance that facilitates **CGMP** compliance – not in "harmonizing" guidances whose foundations are based on systems that fundamentally differ from the required **CGMP** minimums foundation set forth in the **FDC Act**.

Section V. CONTENT OF A COMPARABILITY PROTOCOL

"Part E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?
Page 15, Lines 570-579

We recommend a statement be included in the comparability protocol for changing manufacturing facilities saying that a move to a different drug substance or drug product manufacturing site will be implemented only when the site has a satisfactory CGMP inspection for the type of operation. Furthermore, in the case of aseptically processed product, the statement would also indicate that a move to a different facility or area (e.g., room or building on a campus) will be made only when the specific facility or area has a satisfactory CGMP inspection (irrespective of the overall CGMP status for the campus). For a move to another type of site (e.g., drug substance intermediate manufacturing site, testing laboratory), a statement would be included that the move to this site would not be implemented if there were an unsatisfactory CGMP inspection for the site.

If a change in manufacturing site is proposed for an aseptically processed product, would FDA sanction the site change if the specific facility or area has successfully met a CGMP inspection within two years of when the comparability report is submitted?

If not, would successful media fills (3 lots) be satisfactory evidence if the last inspection period exceeded two years at the time the comparability report is submitted?"

Though this reviewer cannot answer for the **FDA**, he would recommend that, to be approved, the aseptic facility should have its **CGMP** compliance history updated to a date appropriately close to the submission date before the CP is approved.

For example, in the approval, the Agency should require the sponsor to initiate use of that facility within one (1) year of the approval and submit the required CP report, including the results of at least three (3) media fills, within 18 months of the approval or the approval should automatically be suspended pending a facility inspection update.

Given the high risk to the public associated with facilities that aseptically process product, the Agency should do all that it can to ensure that such facilities have an up-to-date, satisfactory, and **CGMP**-compliant inspection history.

Furthermore, this reviewer would recommend changing the sentence by striking the last parenthetical phrase, "Furthermore, in the case of aseptically processed product, the statement would also indicate that a move to a different facility or area (e.g., room or building on a campus)

will be made only when the specific facility or area has a satisfactory CGMP inspection ~~(irrespective of the overall CGMP status for the campus)~~.

This change is suggested to align the guidance with the Agency's "systems-based approach" to site inspection that is supposed to address each site holistically.

"Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?
Page 15, Lines 570-579

In the past, applicants have used protocols for container closure system changes, and they can continue to use them. A comparability protocol can be particularly useful for repetitive container closure system changes.

The guidance states that comparability protocols are useful for repetitive container Closure changes. Does this imply the comparability protocol must be submitted each time for the change?

For example, if a sponsor proposes to change the same rubber stopper for closures on multiple drug products can a single comparability protocol be submitted for all affected drug products?"

While this example could qualify for a single comparability protocol, it is up to the Agency to decide when a) multiple protocols are needed or b) multiple changes may be combined into the same protocol.

Given that a problem with a blanket change for one product in a multiple-product comparability protocol would require all of the products to then be considered under a PAS, perhaps the better use of industry and Agency resources would be to submit multiple CPs (one for each product) under a blanket cover letter ("grouping").

Using this approach, all would be submitted together without linking the fate of the whole to the worst-case outcome that might occur for any one product.

"Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part I. Can a Comparability Protocol Be Included in a DMF or VMF?
Page 16, Lines 610-617

A comparability protocol can be included in a master file. The protocol can be cross-referenced for CMC changes. An applicant's submission must include a letter authorizing the FDA to review the master file (e.g., 21 CFR 314.420(b)). Comparability protocols are product specific. Therefore, the applicant's submission would provide a comparability protocol that augments the information provided in the master file by specifying, for example, any additional studies that will be performed to demonstrate suitability of the postchange material (e.g., conformance to approved specification, compatibility studies, stability studies). The FDA ordinarily neither independently reviews master files nor disapproves submissions to a master file.

By what regulatory mechanism would a sponsor know if their comparability protocol was approved if the protocol is imbedded within a Drug Master File, which FDA neither approves nor disapproves?"

Under the current mechanisms governing DMF/VMF submissions, the DMF/VMF holder's submission of a Comparability Protocol (CP) to an Agency would not even be reviewed until a review-triggering event occurred.

Then, when the review found the protocol acceptable, the holder and, if there is one, their legally authorized US agent, the protocol would not be approved.

However, the current triggering mechanism would require a drug product manufacturer who wanted to use the product to submit a referencing filing.

This reviewer would propose that this guidance could modify that triggering mechanism simply by stating that:

1. A the review of a CP submitted to a DMF/VMF would not be initiated until and unless the DMF/VMF documents filed with the Agency contain both the CP protocol (CP-P) following or equivalent to the guidances requests and a CP report (CP-R) that includes sufficient full-scale batches and their information and data to fully support the fact that the post-change product is comparable to the pre-change product.
2. When the firm has met Condition 1, a CP protocol/report (CP-P/CP-R) review will be initiated whenever the DMF/VMF holder of an accepted, listed drug substance submits a letter that a) requests that that CP-P/CP-R set be reviewed and authorizes the Agency to review those portions of the filed DMF/VMF documents necessary for the Agency to effectively review that CP-P/CP-R.

An Agency "CP-P/CP-R" acceptance letter would state that, based on Agency review and subject to continued **CGMP** compliance, product made using the changes in the CP-P could be shipped provided each batch is made and controlled under a quality system that ensures **CGMP** compliance.

Similar, an Agency "CP-P/CP-R" rejection letter would state that, based on Agency review of the firm's CP-P and CP-R, product made using the changes proposed is not acceptable (because ...), lots made using the changed process are not **CGMP**, and cannot be shipped for use in **FDA**-approved drug products.

Given that DMFs/VMFs are "trade secret" documents, all firms that list the DMF/VMF holder as a component source can and should be notified of is, in rejection cases ONLY (because they are of a for cause nature), that DMF/VMF holder product made by any process other than that accepted by the Agency cannot be used in their drug products.

As it is today, it would then be up to the purchasing firm, upon the receipt of that rejection letter, to address any issues associated with that notice with the DMF/VMF holder or their authorized agent.

What is Draft text seems to be intended to do is to remind the drug product manufacturer to have a strong contractual and working agreement with their DMF/VMF-holder suppliers and work with them to ensure that any of the changes the component manufacturer makes do not adversely impact the drug product produced from said drug substances.

This could be one of the Agency's not so subtle ways of reminding the drug product manufacturer that they, not the Agency, bear the responsibility and accountability for the risks they elect to take. [**Note:** If a DMF/VMF holder will not, for a fair price mark up, agree to provide the information needed by the drug product manufacturer and work with that firm to address that drug product firm's specification requirements and change issues, the drug product manufacturer should simply not buy that component from that source.]

"Would a comparability protocol first be submitted for approval and then incorporated into the DMF?"

Doing what the commenters propose would make public the Comparability protocol, provide FOIA access to information that in other documents is considered a

"trade secret," and prevent the DMF/VMF holder from incorporating it into the "trade secret" DMF/VMF file.

Based on the preceding realities, this reviewer does recommend that the Agency not pursue their suggested course of action.

Centacor, Inc.'s Submission, Dated June 24, 2003, To Docket 03D-0061: "C-04"

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

These commenters begin by stating, "The draft guidance, according to the notice issued at the time of publication is intended to provide guidance for industry on preparing and using comparability protocols for post approval changes in chemistry, manufacturing and controls (CMC). Detailed specific comments on the draft guidance are attached. We appreciate the opportunity to provide comments on this guidance and are committed to collaborating with the Agency to develop improved versions of the guidance."

Section	Line	Comment	Rationale
I	41	Please clarify the definition of equivalence. Thisr eviewer doesn_ot agree with this comment. What is needed instead is to remove the term "equivalence," substitute the term "comparability," and define the word "comparable." This is the case because this guidance's goal is, as the title, indicates to establish drug substance and drug product "comparability," which is possible, and not equivalence," which, *while semantically possible*, is not, in reality, attainable. While the products produced by two related processes (pre-change and post-change) may be comparable, they cannot be truly equivalent. This is the case, if for no otherr eason, because the products were not produced by the same exact process. From the viewpoint of scientific equivalence, the validity of the previous remark is, or should be, self-evident.	The term equivalence should be further defined as provided in the FDA Guidance for Industry "Changes to an Approved NDA or ANDA", Section IV.B. This reviewer does not agree. All uses of the word "equivalence" and "equivalent" should be replaced with the "comparability" and "comparable," respectively and the term "comparable" defined as follows: "**Comparable:** For the purposes of this guidance, alternative processes and products produced by alternative processes are deemed comparable to the original **FDA**-accepted process if and only if the alternatives and their products have been shown to meet all their existing safety parameters, and identity, strength, quality, and purity specifications as well as all of the applicable **CGMP** requirements that appertain thereto." Proposed Draft changes: **Table of Contents** and **Lines 127-128**: "D. Where Can More Information on Postapproval Changes and Demonstration of ~~Equivalence~~ **Comparability** Be Found?" **Lines 42-44:** Such an assessment often includes demonstration that ... are ~~equivalent~~ comparable. **Lines 133-135:** "The following guidances provide ... information on (1) demonstrating ~~equivalence~~ comparability, (2) ..., and (3) ..." **Lines 368-369:** "A comparability protocol should include a plan ... to demonstrate the ~~equivalence~~ comparability of pre- and postchange product." **Lines 419-421:** "You should include ... and/or demonstrate ~~equivalence~~ comparability between pre- and postchange material." **Line 463:** "7. ~~Equivalence~~ **Comparability** Not Demonstrated Using the Approved Comparability Protocol" **Lines 465-468:** "It is anticipated that some changes ... will result in a postchange product that cannot be demonstrated to be ~~equivalent~~ comparable to the prechange product without ..."

Section	Line	Comment	Rationale
II	94	Safety or effectiveness	For consistency throughout document. This reviewer agrees with the commenters' suggested correction.
III	150-151	Please provide examples of "cases" which would allow reduction of more than one reporting category.	To clarify the Agency's expectations and guidance in this area.
IV	271	Safety or effectiveness	For consistency throughout document.
IV	288-290	The requirement for a prior approval supplement (PAS) for a revised protocol is restrictive and should be reconsidered. This reviewer agrees that requesting a firm to submit a PAS when a protocol is revised is restrictive. However, this reviewer does not see where the guidance lines cited require that action in all cases. In fact, the section (**Lines 283-295**) titled, "**D. When Does a Comparability Protocol Become Obsolete?**", the Draft (**Lines 294-295**) states, "**If you find the comparability protocol is no longer correct or adequate, the current protocol should be modified or withdrawn,**" but does not state exactly how to submit the modification. Unless **a)** the modification is a sponsor's analytical test method change "imposed" by a change in a compendial or other such **FDA**-recognized method and **b)** the sponsors analytical method is explicitly tied to the source method or **c)** the change is dictated by an FDA regulatory change, all modifications to approved CPs are obviously PAS changes. This is the case because they are being made based on an improved understanding of the process or because, in reality, some study has shown that one or more of the approved changes will probably lead to post-change product that is not comparable to pre-change product. Firms do not, on their own initiative, change approved protocols of any kind unless they become aware that the protocol is somehow invalid. For second and third-party mandated changes, this reviewer would propose that such be treated as CBE-30 submissions to give the Agency time to ensure the changes proposed in the submission are only changes imposed by a legally binding second or third party mandate.	Depending on the modification to the protocol, a CBE or CBE30 may be an appropriate mechanism for submission of a revised protocol. For example, if the protocol incorporates a change in an analytical method procedure that provides the same or increased assurance of the identity, strength, quality, purity or potency of the material being tested, perhaps submission of a revised protocol via a CBE or CBE-30 is appropriate. At best, this reviewer can only partially agree with what the commenters are proposing. If the change in the protocol is on the sponsor's initiative, then the change should be PAS because firms do not make such changes unless the results of some study indicates that the sponsor's current controls are in some respect less than adequate for the purposes intended. Only when the "example" analytical method change is mandated by an **FDA**-recognized third party (e.g., ***USP***) is it appropriate to consider any lesser reporting category for the modified protocol. Even in such cases, the reduction should not be automatic. The reduction in classification should only be granted when the sponsor provides proof that the results obtained by the ***USP***-revised method are comparable to the results obtained by the method used for the review and approval of the now-approved comparability protocol. All other revisions to an approved comparability protocol should be PAS because they indicate a lack of process understanding upon the part of the submitter. Moreover, such revised comparability protocols should trigger a review of not only the proposed revision, its supporting data and justification documentation but also a revisiting of the original approved comparability protocol's submission package to ensure the overall submission: **a)** is still **CGMP** compliant and **b)** still predicts that the post-change product will be comparable to the pre-change product. For example in cases a reduction is warranted, the commenters' suggestions do not differentiate between: **a)** what should be done to change a comparability protocol when the comparability protocol is submitted but not yet approved and **b)** what should be done when the change is to an approved comparability protocol.

Section	Line	Comment	Rationale
IV (Cont.)	288-290 (Continued)	Furthermore, in such cases, this reviewer would recommend that the Agency should request the sponsor to provide the appropriate bridging data to show that such modifications have the same or better probability of producing comparable product as the changes in the approved CP.	In case "a)," this reviewer would agree with the general reporting of the change (in this, in the Annual Report) but would suggest that the sponsor submit the update to a protocol under review as an addendum. When the validity of the categorization of the change is verified and the supporting data submitted are found to support the applicable submitted specifications, the Agency should simply incorporate the change as a modification to the protocol and proceed as though no modification had been made. In cases where the data submitted does not support the existing specifications, the development of a scientifically sound and appropriate PAS filing should be initiated. In case "b)," this reviewer would propose two courses of action. *For approved comparability protocols that have not yet been executed*, the Agency should require the sponsor to consider the approved comparability protocol as obsolete and to submit a modified comparability protocol that, for such modifications, could be given expedited review status. *For approved protocols whose execution has been initiated*, the Agency should direct that sponsors complete the protocol using both test procedures from the point the change is implemented and report both sets of data along with the reason for the change in method. In both instances supporting data should be submitted with the changes proposes. In cases where the method changes lead to comparable findings, the sponsor can proceed as if the modification had not been made. In any case where the data submitted do not support the existing specifications, the development of a scientifically sound and appropriate PAS filing should be initiated. [**Note:** For sponsor initiated changes, the Agency should require the sponsor to obsolete the current protocol and submit the modified protocol along with an appropriate body of evidence and justification that support the changes being sought.]

A Review of Formal Comments To Public Docket 03D-0061

AstraZeneca Pharmaceuticals LP's Submission, Dated June 16, 2003, To Docket 03D-0061: "C-03"

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

These commenters begin by stating, "Reference is made to the Federal Register availability notice issued on February 25, 2003 for the Draft Guidance for Industry on Comparability Protocols - Chemistry, Manufacturing, and Controls Information. AstraZeneca has reviewed this draft guidance and our comments are as follows:"

Line(s)	Comment
86 - 91	For consistency AstraZeneca (AZ) suggests putting the listed changes in the same order as in the SUPAC guidance-whenever possible.
86 - 91	AZ suggests adding "specifications", "stability protocols", "expiration period extensions" and "other changes". This reviewer has no problems with adding the bullet items that the commenters are suggesting, but would also suggest adding "components" and "controls."
89	AZ suggests changing "manufacturing facilities" to "manufacturing sites" in order to remain consistent with SUPAC. This reviewer disagrees and, as an alternative, suggests keeping "manufacturing facilities" (which differ from the site) adding a bullet for "manufacturing sites" to the list in the Draft.
101	AZ recommends inserting "(for example, a stability study)" after the word "study" in order to give an example. In principle, this reviewer agrees with the commenters' suggestion. However, to ensure **CGMP** compliance, this reviewer suggests changing the sentence (**Lines 99 – 103**) to read as follows: "**A comparability protocol describes the changes that are covered under the protocol and specifies the ~~tests~~** specifications, standards, representative-sample sampling plans, test procedures, and other controls that will be used, the **studies** (e.g., active uniformity, active availability, impurity, pH,p urity, clarity, fill volume, weight variation, hardness, etc.) **that will be performed, ~~including the analytical procedures that will be used~~,** and the **acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product.**"
130 -132	AZ recommends inserting a statement that this guidance may supersede other FDA guidance documents for filing strategy. This reviewer finds the commenters' suggestion but suggests that their suggestion should be expanded into the following general statements: "When this guidance and other prior guidances seem to be in conflict, the provisions in this guidance shall supersede the relevant text in the prior guidance. However, nothing in this guidance is intended to supersede the requirements for **CGMP** compliance."
150	AZ suggests inserting "future" before "CMC changes". This reviewer disagrees with the commenters' suggested change and suggests adding the phrase "the proposed" before "CMC changes."
156 - 157	Please provide examples of a potential 2 step change, for example, a container/closure change. This reviewer supports the inclusion of examples.
164	Please add: "...of a repetitive nature, **for example, container/closure.**" This reviewer has no problem with the text provided it is modified to restrict it to a single product as follows: "**A comparability protocol can be particularly useful for changes of a repetitive nature,** for example, a container and/or closure change for a single drug product."

Line(s)	Comment
170- 171	AZ recommends replacing this sentence with "We recommend that comparability protocols be considered only for CMC changes that applicants anticipate will be made that may qualify for reduced filing burden. This reviewer has no problem with the commenters' recommendation, but would leave it up to the Agency to decide the wording that should be used here.
190 - 192	AZ suggests that FDA should refer to the Acceptance Criteria (starting line 416) in order to allow for changes that result in-adjustments to the specifications. This reviewer does not agree with the commenters' proposal for several reasons. The most important of which is the attempt to equate specifications with acceptance criteria. Though related, "specifications" and "acceptance criteria" are not at all the same. "Specifications" are the limits and/or ranges that each of the batch-representative samples tested must meet before a batch can be evaluated for its acceptability. "Acceptance criteria" are the derived statistical values calculated from the measured sample values that predict, at some percentage and confidence levels, that the batch of untested materials or units would, if tested, will meet the acceptance criteria (for discrete units, these are usually expressed in terms of an acceptable quality limit [AQL] for the allowed maximum % of non-conforming units).
192 - 194	Please clarify what level of validation is required and state if analytical validation data is expected to be submitted with the validation protocol. Though this reviewer cannot speak for the Agency, he recommends that; a) the level of validation or qualification should be no less than the **CGMP** regulations require for each batch (**21 CFR 211**) and b) the validation protocol, validation report, the test records and data should be submitted in the Comparability Protocol.
244 - 250	AZ Recommends Inserting A Second Bullet - "A Prior Approval Supplement That Contains Data Obtained From A Small-Scale Process Or Other Studies Incorporating The Proposed Change To Provide Preliminary Evidence That The Change Is Feasible, As Well As Preliminary Information On The Effect Of The Change On The Product. This Reviewer has problems with this insertion because this reviewer thinks that all comparability protocols (CPs) should contain the supporting studies that these commenters have proposed as one PAS option to wrap around CPs. Since this is a possible option, this reviewer leaves it up to the Agency to decide if such a PAS, essentially a naked CP PAS should be proposed as an option.
246 - 250	This description seems indistinguishable from a standard prior approval supplement. This reviewer disagrees with the commenters' statement because the inclusion of a comparability protocol (CP) in and of itself makes it different from a standard PAS that may contain the same exact information without the CP. The inclusion of the CP provides the logical framework for the changes and the justification thereof that the sponsor is proposing to introduce into their process as well as, hopefully, the supporting data that led the sponsor to propose the exact changes, specifications, representative-sample sampling plans, test procedures, studies and acceptance criteria that the CP sets forth. Can a sponsor submit a comparability protocol and sNDA simultaneously? Though this reviewer cannot answer for the Agency, this reviewer's answer is that, while you may submit a comparability protocol that is part of an sNDA, the Draft guidance, as written (given the preceding text), does not support the submission of a standalone CP.
294 - 296	Please consider allowing the modification of an existing (approved) protocol via an annual report. This reviewer has considered the commenters' proposal (see previous comment sections) but only supports this option for the case where: **a)** the "modification" being sought is to an approved CP whose execution has not been initiated and **b)** the "modification" is an FDA-recognized third-party-mandated revision (e.g., ***USP*** or ***AOAC International*** official method or official specification revision) to a scientifically sound and appropriate test method or specification that the sponsor has directly **tied** (linked) to said third-party revision. Otherwise, this reviewer is opposed to using an AR to report: **a)** modifications initiated for other reasons or **b)** modifications initiated after the execution of an approved CP has begun.

Line(s)	Comment
300	AZ recommends inserting "unless otherwise provided for in this guidance" after the word "application". This reviewer is opposed to the commenters' recommendation because that latitude, *if needed at all*, should be provided in the referenced section, "IV. A." and not here.
315 - 316	AZ recommends the following first sentence: "Editorial or minor changes (i.e. alternate methods) can also be made." This reviewer is opposed to this and any other language that attempts to establish subjective levels of modifications (such as the "minor changes" language that the commenters are attempting to insert here). Moreover, this reviewer notes that editorial changes are discussed later in this section. Therefore, the commenters' recommendation should simply be ignored in this instance.
425 - 436	This paragraph is confusing. If a PAS is required for a specification change as per "Changes to approved ANDA or NDA" guidance, the draft guidance indicates the firm should file as a PAS. If "Changes to approved ANDA or NDA" says that a lesser filing category is required, a firm can use the comparability protocol (which is a PAS) to get approval of a specification change that could otherwise be approved without the submission of a PAS. AZ suggests that FDA may want to clarify the intent of this paragraph. This reviewer agrees and would recommend the commenters read the proposals made by this reviewer and other commenters in the comment sections prior to this one that address this issue.
439 - 443	AZ suggests that this paragraph/sentence should end at "...is reported to FDA." This reviewer does <u>not</u> agree. However, as he has before, this reviewer would again recommend that this long sentence be cast in a different (semi-outline form). To that end, this reviewer again proposes: "The comparability protocol should identify the ~~following~~ information~~, which~~ that will be submitted to the FDA at the time a post approval CMC change is implemented under an FDA-approved comparability protocol. At a minimum, that information should, include the following: 1. ~~the~~ Type of data (e.g., in-process, release, long-term or accelerated stability data) 2. ~~the~~ Amount of data (e.g., release data from two (2) full-scale and three (3) pilot-scale batches, 3-months of accelerated stability data) 3. ~~the~~ Data that will be generated prior to distribution of the changed product (e.g., in-process and release data from not less than three [3] full-scale batches, or 3 months of accelerated stability data and 3-month's long-term-storage-condition data on not less than 3 full-scale batches), where appropriate (e.g., when the proposed reporting category is a CBE-30, CBE-0, or AR)."

MedImmune Inc's Submission, Dated June 2, 2003, To Docket 03D-0061: "C-02"

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

These commenters begin by stating, "Please find enclosed MedImmune's comments on the Draft Guidance on 'Comparability Protocols - Chemistry, Manufacturing, and Controls Information.'"

[**Note:** The page numbers in the commenters' "annotations" listing are, for some reason, one less than the page numbers displayed in this reviewers viewing of the commenter's ".pdf" file. In addition, the line numbers in the commenters' file do not always match those in the published Draft. To address these realities, this reviewer has put the commenters' *page* and, where they differ, *line numbers* in italicized text to identify that they are peculiar to the Draft text submitted by MedImmume's commenters (apparently, their comments are to an earlier draft). Similarly, the commenters' **proposed modifications or additions** are **bolded** to differentiate them from the text in the original draft.]

Page *6*

Lines 20-25

"Annotation 1; Label: Medimmune Medimmune; Date: 2/24/2003 4:28:34 PM
The guidance applies to 22 comparability protocols that would be submitted in new drug applications (NDAs), abbreviated new 23 drug applications (ANDAs), new animal drug applications (NADAs), abbreviated new animal 24 drug applications (ANADAs), or supplements to these applications, except for applications for protein products 2 24. Well-characterized synthetic peptides submitted in these applications are included within the scope 25 of this guidance."

Location in published Draft: **Lines 21-25**

This annotation does <u>not</u> appear to change anything vis-à-vis the published Draft.

"Annotation 2; Label: Medimmune Medimmune; Date: 2/24/2003 4:29:07 PM
Why doesn't this guidance apply to BLAs?"

"**Page** *10*

Line *143*

"Annotation 1; Label: Medimmune Medimmune; Date: 2/24/2003 4:30:33 PM
achieved

Annotation 2; Label: Medimmune Medimmune; Date: 2/24/2003 4:31:1 I PM
Clarification: 'met' instead of 'achieved'"

Location in published Draft: **Lines 148-150**

While this reviewer has no problems with the commenters "clarification," this reviewer would again revise the Draft sentence to read:

"A comparability protocol should *prospectively* specify how the effects of the proposed CMC changes will be assessed (i.e., the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be achieved to assess the effect of CMC changes) and supply the scientifically sound basis data that establishes the proposed changes: a) will maintain full **CGMP** compliance, b) are scientifically sound, and, for drug products, c) comply with statistical process control requirements set forth in **21 CFR 211.165(d)**."

Line *145-148*

"Annotation 3; Label: Medimmune Medimmune; Date: 2/24/2003 4:32:02 PM
Clarification: 'particular' instead of specified

Annotation 4; Label: Medimmune Medimmune; Date: 2/24/2003 4:33:14 PM
...in a lower category than if the change were to be implemented without an approved comparability protocol.

Annotation 5; Label: Medimmune Medimmune; Date: 2/24/2003 4:33:27 PM
in a category lower than the *147* category for the same change, were the change to be implemented without an approved comparability *148* protocol."

Location in published Draft: **Lines 152-154**

While this reviewer agrees, in principle, with the first change proposed in this sentence, this reviewer again recommends changing this sentence to read:
"Using the information and data submitted by the manufacturer, the Agency will be able to determine if the proposed changes submitted in a Comparability Protocol will reduce the reporting and/or review requirements vis-à-vis the same changes submitted via an Agency-acceptable filing that lacks a comparability protocol."

Lines *148-150*

"Annotation 6; Label: Medimmune Medimmune; Date: 2/24/2003 4:34:26 PM
...are one level lower than normally would be expected...

Annotation 7; Label: Medimmune Medimmune; Date: 2/24/2003 4:34:55 PM
one category lower than normally would be the case"

Location in published Draft: **Lines 154-156**

While this reviewer recognizes that the notes make no change, this reviewer would again recommend the sentence containing the text in question be revised to:
"Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g., from PAS to CBE-30; from CBE-30 to CBE; or from CBE to AR)."

Lines *138-153*

"Annotation 8; Label: Medimmune Medimmune; Date: 2/24/2003 4:35:26 PM
you have

Annotation 9; Label: Medimmune Medimmune; Date: 2/24/2003 4:35:42 PM
Delete 'you have'

Annotation 10; Label: Medimmune Medimmune; Date: 2/24/2003 4:38:19 PM
...particular product or process (or similar products or processes) be gathered so the appropriate tests, studies, analytical procedures, and acceptance criteria can be defined. In this way, a clear rationale shall be defined for demonstrating that the CMC...

Annotation 11; Label: Medimmune Medimmune; Date: 2/24/2003 4:38:32 PM

or similar products or processes so you can specify a priori the tests, 162 studies, analytical procedures, and acceptance criteria appropriate for demonstrating that the CMC"

Location in published Draft: **Lines 165-170**

This reviewer recommends that the Draft remain as it is – with the "you have" phrase that these commenters apparently would remove.

Page *11*

Lines *181-185*

"Annotation I; Label: Medimmune Medimmune; Date: 2/24/2003 4:39:18 PM
specifications and *183* appropriate and sensitive analytical procedures have been established and validated or qualified

Annotation 2; Label: Medimmune Medimmune; Date: 2/24/2003 4:40:21 PM
...drug product specifications. Appropriate and sensitive analytical procedures must be established and validated/qualified..."

Location in published Draft: **Lines 190-194**

This reviewer agrees with the only apparent change that the commenters make – splitting a long sentence into two parts as indicated in "Annotation2" and would recommend the following revisions:

"In general, we recommend that a comparability protocol be considered only if the product resulting from the changes is expected to meet the approved drug substance and/or drug product specifications. ~~**and appropriate and sensitive**~~ Moreover, scientifically sound and appropriate **analytical procedures should have been established and validated or qualified (i.e., for nonroutine tests such as characterization studies)** to be able to **detect the effect of the change on the approved product."**

Page *12*

Lines *220-222*

"Annotation 1; Label: Medimmune Medimmune; Date: 2/24/2003 4:41:06 PM
...move to a new manufacturing site...

Annotation 2; Label: Medimmune Medimmune; Date: 2/25/2003 8:45:58 AM
to a manufacturing"

Location in published Draft: **Lines 229-231**

This reviewer notes that the net effect of the commenters' annotations appears to be no substantial change.

Thus, this reviewer does not understand why these annotations were left in the document.

Page *13*

Lines *237-240*

"Annotation 1; Label: Medimmune Medimmune; Date: 2/24/2003 4:42:26 PM
...proposed comparability protocol, test, and study...

Annotation 2; Label: Medimmune Medimmune; Date: 2/24/2003 4:42:48 PM
insert period at end.

Annotation 3; Label: Medimmune Medimmune; Date: 2/25/2003 8:46:20 AM
proposed comparability protocol"

Location in published Draft: **Lines 246-250**

This reviewer notes that the net effect of the commenters' annotations appears to be no substantial change.

Thus, this reviewer does not understand why these annotations were left in the document.

Lines *241-242*

"Annotation 4; Label: Medimmune Medimmune; Date: 2/25/2003 8:46:27 AM
and test"

Location in published Draft: **Lines 251-252**

This reviewer does not agree with the commenters' addition.

Page *16*

Lines *372-373*

"Annotation 1; Label: Medimmune Medimmune; Date: 2/24/2083 4:44:33 PM
. . .would be chosen that are capable of detecting new impurities or other significant changes in a product...

Annotation 7; Label: Medimmune Medimmune; Date: 2/25/2003 8:47:02 AM
chosen *373* capable of detecting new impurities or other changes in a product that can result from the change"

Location in published Draft: **Lines 386-388**

This reviewer disagrees with the changes because, as written, the sentence is not logical.

This reviewer recommends the following revision to improve the logic of the sentence:

"~~Analytical~~ The analytical **procedures** chosen ~~would~~ should **be** ~~chosen~~ **capable of detecting new impurities or other** variable factor **changes** ~~in a product~~ **that** ~~can result from~~ may be caused by **the** ~~change~~ changes proposed."

Lines *376-378*

"Annotation 2; Label: Medimmune Medimmune; Date: 212412003 4:46:19 PM
. . .analytical procedures can be used to monitor the . . .

Annotation 8; Label: Medimmune Medimmune; Date: 2/25/2003 8:47: 16 AM
be called for to"

Location in published Draft: **Lines 391-393**

This reviewer finds that the commenters' suggestions match the Draft text but would suggest that the text could be improved as follows:

"**For example, revised or new analytical procedures** ~~can be called for~~ may be needed **to monitor the removal of a new process impurity generated by a new manufacturing process.**"

Lines *382-383*

"Annotation 3; Label: Medimmune Medimmune; Date: 2/24/2003 4:46:44 PM
Validation of newly modified...

Annotation 9; Label: Medimmune Medimmune; Date: 2/25/2003 8:47:23 AM
new"

Location in published Draft: **Lines 397-398**

This reviewer disagrees with the commenters' remarks and the Draft's text here.

This reviewer proposes the following alternative:
"~~Validation~~ The initial validation of new modified analytical procedures or ~~revalidation~~ the on-going validation or verification of existing analytical procedures should be performed, as appropriate."

The preceding modification meshes with the **CGMP** view that validation is a journey and not a destination.

Lines *383-386*
"Annotation 4; Label: Medimmune Medimmune; Date: 212412003 4:49:55 PM
The protocol would specify the use of new or revised analytical procedures and the appropriate validation or revalidation information; the information can be provided when a postapproval CMC change, which has been implemented using the approved...

Annotation 10; Label: Medimmune Medimmune; Date: 2/25/2003 8:47:37 AM
specify that any new or revised analytical 384 procedures and the appropriate validation or revalidation information would be provided when a 385 postapproval CMC change implemented using the approved comparability protocol is reported to 386 FDA."

Location in published Draft: **Lines 398-401**

This reviewer again would propose alternative the following alternative text:
"The protocol ~~would~~ should specify that any new or revised analytical procedures and the appropriate validation ~~or revalidation~~ and/or verification information would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA (i.e., reported in an AR, CBE-0, CBE-30, or PAS, as appropriate)."

Lines *390-392*
"Annotation 5; Label: Medimmune Medimmune; Date: 212412003 4:50:46 PM
...release testing, it is not necessary to report changes...

Annotation 11; Label: Medimmune Medimmune; Date: 2/25/2003 8:47:57 AM
you do not have"

Location in published Draft: **Lines 405-407**

This reviewer notes that the commenters' proposals seem to match the Draft's text.

Lines *392-396*
"Annotation 6; Label: Medimmune Medimmune; Date: 212412003 4:52:53 PM
...these analytical procedures are described as part of a comparability protocol, then any new or revised procedures and, as appropriate, results from validation or qualification studies for any modified procedure would be reported to FDA when a postapproval CMC change is implemented using the approved comparability protocol.

Annotation 12; Label: Medimmune Medimmune; Date: 2/25/2003 8:48: 12 AM
specified in and *393* provided as part of a comparability protocol, any new or revised analytical procedures and, as *394* appropriate, results from validation or qualification studies for any modified procedure would be *395* provided when a postapproval CMC change implemented using the approved comparability protocol is *396* reported to FDA."

Location in published Draft: **Lines 407-411**

This reviewer notes that the sum of the commenters' annotations seem to match the Draft's text.

As an alternative, this reviewer proposes the following:

"~~However, if~~ When these analytical procedures are specified in and provided as part of a comparability protocol and a postapproval CMC change implemented using the approved comparability protocol is reported to FDA, the sponsor should provide the following in that report:

- ~~any~~ Any new or revised analytical procedures and,
- ~~as appropriate,~~ The results and data, if any, from the validation or ~~qualification~~ verification studies for any modified procedure"

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Lines *404-406*

"Annotation 1; Label: Medimmune Medimmune; Date: 2/24/2003 4:54:12 PM
The acceptance criteria (numerical limits, ranges or other criteria) should be included for each specified..."

Location in published Draft: **Lines 419-424**

This reviewer does not support the suggested change because, where possible, the use of the active voice (as in the Draft) is preferred to the use of the passive voice (as the commenters' annotation suggests).

Lines *410-419*

"Annotation 2; Label: Medimmune Medimmune; Date: 2/24/2003 4:54:27 PM
If implementing a change using a comparability protocol calls for a revision of the drug product or drug 13 411 substance specification, we recommend you consider the recommended reporting category for the 412 type of specification change as well as the designated reporting category for reporting a change using 413 your comparability protocol. When the recommended reporting category for the specification change is 414 higher (e. g., PAS) than the reporting category for changes made under the comparability protocol (e. g., 415 CBE- 30), the change would be reported as recommended for the specification change. If the 416 recommended reporting category for the specification change is the same or lower than the designated 417 reporting category for changes made under the comparability protocol, the specification can be updated 418 and provided when a postapproval CMC change implemented using the approved comparability 419 protocol is reported to FDA."

Location in published Draft: **Lines 426-429**

This reviewer notes that the commenters' annotation seems to match the Draft's text.

Lines *423-427*

"Annotation 3; Label: Medimmune Medimmune; Date: 2/24/2003 4:55:00 PM
This entire paragraph is fuzzy. It is unclear what is being said.

Annotation 4; Label: Medimmune Medimmune; Date: 2/24/2003 4:56:20 PM
...is reported to FDA. When appropriate, indicate whether the data will be generated prior to distributing the product made with the change...

Annotation 5; Label: Medimmune Medimmune; Date: 2/24/2003 4:56:41 PM
Delete the word 'proposed'

Annotation 6; Label: Medimmune Medimmune; Date: 2/25/2003 8:48:38 AM
You should include the acceptance criteria

Annotation 7; Label: Medimmune Medimmune; Date: 2/25/2003 8:48:52 AM
and, when *426* appropriate, generated prior to your distributing the product made with the change (e.g., when *427* proposed reporting category is a CBE- 30, CBE- 0, or AR)."

Location in published Draft: **Lines 440-444**

Again, this reviewer does not agree with either the commenters' annotation or with the Draft's text.

As other commenters' have stated the sentence is too long and complex to be easily grasped and needs to be restructured to improve the reader's ability to comprehend the message being conveyed.

To do this, this reviewer recommends the following:

"The comparability protocol should identify the ~~following~~ information~~, which~~ that will be submitted to the FDA at the time a post approval CMC change is implemented under an FDA-approved comparability protocol. At a minimum, that information should, include the following:

1. **~~the~~** Type **of data (e.g., in-process, release, long-term or accelerated stability data)**
2. **~~the~~** Amount **of data (e.g.,** release data from two (2) full-scale and three (3) pilot-scale batches, **3-months of accelerated stability data)**
3. **~~the~~** Data **that will be generated prior to distribution of the changed product** (e.g., in-process and release data from not less than three [3] full-scale batches, or 3 months of accelerated stability data and 3-month's long-term-storage-condition data on not less than 3 full-scale batches), **where appropriate (e.g., when the proposed reporting category is ~~a~~ CBE-30, CBE-0, or AR)."**

Lines *429-430*
"Annotation 8; Label: Medimmune Medimmune; Date: 2/25/2003 8:48:59 AM
Proposed"

Location in published Draft: **Lines 446-447**

This reviewer notes that the commenters' annotation matches the Draft's text.

"Page *18*

Lines *439-442*
"Annotation 1; Label: Medimmune Medimmune; Date: 2/25/2003 8:21:40 AM
...implemented through the approved...

Annotation 9; Label: Medimmune Medimmune; Date: 2/25/2003 8:49: 13 AM
Using"

Location in published Draft: **Lines 456-458**

This reviewer sees no need to change the Draft as the commenters' first annotation suggests.

Lines *448-452*

"Annotation 2; Label: Medimmune Medimmune; Date: 2/25/2003 8:22:00 AM
...manufacturing process may result...

Annotation 3; Label: Medimmune Medimmune; Date: 2/25/2003 8:23:5 1 AM
...efficacy. or safety testing. In some cases, a product may not meet the prespecified acceptance criteria in the protocol. The protocol should identify the steps that will be taken under such circumstances.

Annotation 11; Label: Medimmune Medimmune; Date: 2/25/2003 8:49:28 AM
or in a product that does *451* not meet the prespecified acceptance criteria in the protocol. You should identify in the protocol the *452* steps you will take in such circumstances."

Location in published Draft: **Lines 465-469**

This reviewer disagrees in part with both the commenters' annotations and the draft text.

This reviewer again proposes to change the text to read:

"It is anticipated that some changes in the manufacturing process will result in a postchange product that cannot be demonstrated to be ~~equivalent~~ comparable to the prechange product without more extensive physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or in a product that does not meet ~~the prespecified~~ its pre-established acceptance criteria in the protocol. You should identify in the protocol the steps you will take in such circumstances."

Lines *456-457*

"Annotation 4; Label: Medimmune Medimmune; Date: 2/25/2003 8:25:20 AM
A commitment should be included in the comparability protocol that indicates it will be updated or withdrawn when it becomes obsolete.

Annotation 10; Label: Medimmune Medimmune; Date: 2/25/2003 8:49:18 AM
will

Annotation 12; Label: Medimmune Medimmune; Date: 2/25/2003 8:49:42 AM
You should include a commitment in your comparability protocol that you will update or withdraw your *457* protocol when it becomes obsolete"

Location in published Draft: **Lines 473-474**

The commenters' annotation seems to be similar to the Draft's text except that the first one uses the passive voice and the second uses the active voice like the Draft..

This reviewer again recommends that the Draft text's use of the active voice is better and that the Draft text should be retained.

Lines *462-463*

"Annotation 5; Label: Medimmune Medimmune; Date: 2/25/2003 8:26:33 AM
...we recommend that the following issues for changes to the manufacturing process be considered, where applicable:"

Annotation 13; Label: Medimmune Medimmune; Date: 2/25/2003 8:49:54 AV

In addition to the general considerations provided in section V. A, we recommend that you consider the *463* following issues for changes in the manufacturing process, where applicable:"

Location in published Draft: **Lines 479-480**

The commenters' annotation seems to be similar to the Draft's text except that the first annotation uses the passive voice and the second the active voice.

This reviewer again recommends that the Draft text's use of the active voice is better and that the Draft text should be retained.

Lines *467-469*

"Annotation 6; Label: Medimmune Medimmune; Date: 2/25/2003 8:27:01 AM
...of the product manufactured using...

Annotation 7; Label: Medimmune Medimmune; Date: 2/25/2003 8:27:40 AM
...of the product manufactured using..."

Location in published Draft: **Lines 484-486**

This reviewer sees no need to substitute the Draft's "produced" with "manufactured" and would recommend retaining the original text.

Lines *475-477*

"Annotation 8; Label: Medimmune Medimmune; Date: 2/25/2003 8:29: 18 AM
...any new impurities or contaminants. Studies should be done to show impurities are removed or inactivated by downstream processing. Any changes in the impurity profile must meet the predefined criteria..."

Annotation 14; Label: Medimmune Medimmune; Date: 2/25/2003 8:50:02 AM
produced

Annotation 15; Label: Medimmune Medimmune; Date: 2/25/2003 8:50: 10 AM
produced

Annotation 16; Label: Medimmune Medimmune; Date: 2/25/2003 8:50: 18 AM
contaminants, or that they are removed or"

Location in published Draft: **Lines 492-494**

Though the commenters' changes make the text easier to read, they also change the intended meaning.

Based on that reality, this reviewer would recommend the following:

"We recommend that attention be given to demonstrating the absence of any new impurities or contaminants. ~~or that they are~~ When such are found, they should be **removed or inactivated by downstream processing. Any changes in the impurity profile ~~would~~** should **meet ~~the predefined~~** their pre-established acceptance **criteria (see section V.A.4)."**

Page *19*

Lines *499-501*

"Annotation 1; Label: Medimmune Medimmune; Date: 2/25/2003 8:30:34 AM
...included that the controls, including...

Annotation 2; Label: Medimmune Medimmune; Date: 2/25/2003 8:37:07 AM
...validated to remove and inactivate impurities...

Annotation 4; Label: Medimmune Medimmune; Date: 2/25/2003 8:50:35 AM

inactivated by downstream processing. Any changes in the impurity profile would
Annotation 5; Label: Medimmune Medimmune; Date: 2/25/2003 8:50:48 AM
controls, including those that have been *500* validated to inactivate and remove impurities or contaminants,"

Location in published Draft: **Lines 518-520**

This reviewer finds that the commenters' annotations are confusing and do not add anything to the text.

However, to properly treat validation as a journey, the Draft should be revised to read:

"We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be ~~revalidated~~ validated for the new production ~~process,i fa ppropriate~~ for both drug substances and drug products to at least the extent required by **CGMP** as set forth in the **21 CFR 211.110**."

Lines *509-512*
"Annotation 3; Label: Medimmune Medimmune; Date: 2/25/2003 8:32:26 AM
...do not significantly affect the capabilities of the methods validation that are relevant to the type of analytical procedure for their intended use.

Annotation 6; Label: Medimmune Medimmune; Date: 2/25/2003 8:57:04 AM"
change characteristics used in methods validation that are relevant to the type of analytical procedure

Location in published Draft: **Lines 528-532**

This reviewer recommends that the Draft text be left as it is in the Draft.

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"Lines *514-516*
Annotation 1; Label: Medimmune Medimmune; Date: 2/25/2003 8:32:57 AM
predefined

Annotation 4; Label: Medimmune Medimmune; Date: 2/25/2003 8:51:23 AM
prespecified

Location in published Draft: **Lines 534-536**

Because, to be **CGMP** compliant, the firm must establish the acceptance criteria they propose to use and not simply specify or define them, this reviewer recommends that the draft text be revised to read:

"A validation plan would have ~~prespecified~~ pre-established acceptance criteria for relevant validation parameters such as precision, range, accuracy, specificity, detection limit, and quantitation limit."

Lines *525-526*
"Annotation 2; Label: Medimmune Medimmune; Date: 2/25/2003 8:33:14 AM
delete 'use of'

Annotation 5; Label: Medimmune Medimmune; Date: 2/25/2003 8:51:28 AM
use of"

Location in published Draft: **Lines 546-548**

The Draft's text needs to be modified to provide for the deletion of a test only when a new test covers a variable factor that was previously measured using a separate method.

This reviewer and sound science both support the following alteration of the text:

"When used for release or process control, use of the new revised analytical procedure should not result in:

1. The deletion of a test that is described in an approved or licensed application or an accepted DMF/VMF unless
   a. The new revised method measures multiple variables in a single test that were previously measured using multiple tests and
   b. The new revised method measures those variables with at least the same limit of quantitation, precision and accuracy as the test methods the new revised method is superseding,

   or
2. The relaxation of any of ~~the~~ their pre-established acceptance criteria that are described in the approved or licensed application or accepted DMF/VMF."

Lines *547-549*

"Annotation 3; Label: Medimmune Medimmune; Date: 2/25/2003 8:33:48 AM
...facilities indicating that a move...

Annotation 6; Label: Medimmune Medimmune; Date: 2/25/2003 8:51:38 AM
Saying

Location in published Draft: **Lines 570-573** *and through* ***Line 579***

This reviewer finds that the Draft text needs to be augmented by adding text to align the guidance with the **CGMP** ***minimums*** "for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess" **(21 CFR 210.1(a))**.

To accomplish this, this reviewer again recommends the following text:

"We recommend a statement be included in the comparability protocol for changing manufacturing facilities saying that a move to a different drug substance or drug product manufacturing site will be implemented only when the site has a satisfactory **CGMP** inspection for the type of operation. Furthermore, in the case of aseptically processed product, the statement would also indicate that a move to a different facility or area (e.g., room or building on a campus) would only be made when the specific facility or area has a satisfactory **CGMP** inspection (irrespective of the overall **CGMP** status for the campus). For a move to another type of site (e.g., drug substance intermediate manufacturing site, testing laboratory), a statement would be included that the move to this site would not be implemented if there were an unsatisfactory **CGMP** inspection for the site."

Given the requirements of the **FDC Act**, the Agency cannot approve a Comparability Protocol ("CP") for a ***facility*** that does not have inspectional confirmation of satisfactory **CGMP** compliance. In cases where a new facility is proposed, the Agency should, as with any other type of PAS, verify the proposed facility's **CGMP** compliance status. In cases where the proposed ***facility*** (not the site)

does not have a history that supports satisfactory **CGMP** compliance, the CP reviewer will notify the Field Inspectorate and work with them to schedule the needed facility inspection. Firms should not submit a CP unless they know that the facility is ready for a prior approval inspection ("PAI") on the day the CP is submitted. [**Note:** CPs that name facilities at which the Agency *subsequently* finds unsatisfactory **CGMP** compliance at the facility named should, if not approved, be rejected and, if approved, have their approval revoked or suspended until the facility attains satisfactory **CGMP** compliance status.]"

FAME System's Submission, Dated June 2, 2003, To Docket 03D-0061: "C-01"

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

This commenter begin by stating, "The comments being provided to Docket: "03D-0061" are based on a second reading and review of " Draft Guidance for Industry on Comparability Protocols — Chemistry, Manufacturing, and Controls Information [\\CDS029\CDERGUID\5427dft.doc – 02/13/03]" 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. ...

These comments are being submitted with the hope that they will encourage the United States Food and Drug Administration (**FDA**) to require that any submission first be *scientifically sound* and *appropriate*, and second *fully comply* with all of the applicable **CGMP** *minimum* requirements set forth in **21 CFR 211**.

In addition, any guidance document should fully comply with all applicable regulations because, in 1988 in *Berkowitz v. US*, the United States Supreme Court held that an **FDA** administrator has no latitude with respect to any clearly written statute or regulation.

To facilitate differentiation between the proposed alternative and the **FDA**'s Draft, the changes will be in **Lydian** or **highlighted Lydian** font and the **FDA** draft will be in the **Perpetua** font. With the preceding in mind, let us proceed to review the proposed draft."

Line Range	Proposed Text	FDA Draft Text
95-103	**A. What is a Comparability Protocol?** A comparability protocol must be a ***scientifically sound and appropriate***, well-defined, detailed, written plan for assessing the effect of specific CMC changes **in** the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product **and compliance with the applicable CGMP regulations**. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and the **CGMP-compliant** acceptance criteria that must be achieved to demonstrate that specified CMC changes do not adversely affect the product. **Though the** submission of a comparability protocol is optional, **it is recommended that one be submitted whenever a written submission is required prior to effecting a change**. This reviewer recommends changing the phrase "... specific CMC changes in the ..." to "... specific CMC changes ~~in~~ on the ..." This is a grammar correction.	**A. What is a Comparability Protocol?** A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is optional.

Line Range	Proposed Text	FDA Draft Text
127-135	**D. Where Can More Information on Post-approval Changes and Demonstration of Equivalence Be Found?** This guidance, once finalized, is not intended to supersede **the applicable CGMP regulations governing drugs and drug products or** other FDA guidance documents, rather it supplements them with information on using comparability protocols to implement post-approval CMC changes. We recommend that applicants consult **the CGMP regulations for compliance first and then** all relevant guidances[1] for information relating to postapproval changes. The following guidances provide especially relevant information on (1) demonstrating equivalence, (2) documentation to be provided to support post-approval changes, and (3) the recommended reporting categories. This reviewer suggests adding the sentence, "In cases where the recommendations in this guidance conflict with those in a prior guidance, this guidance should supersede the prior guidance," after the first sentence.	D. Where Can More Information on Postapproval Changes and Demonstration of Equivalence Be Found? This guidance, once finalized, is not intended to supersede other FDA guidance documents, rather it supplements them with information on using comparability protocols to implement postapproval CMC changes. We recommend that applicants consult all relevant guidances[2] for information relating to postapproval changes. The following guidances provide especially relevant information on (1) demonstrating equivalence, (2) documentation to be provided to support postapproval changes, and (3) the recommended reporting categories.
165-170	We recommend that you have sufficient **process-representative** manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and **the scientifically sound and appropriate CGMP-compliant** acceptance criteria appropriate for demonstrating that the CMC change or changes will still fully comply with all of the applicable **CGMP** requirements, are based on recognized standards and sound science, and will not adversely affect the product.	We recommend that you have sufficient manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and acceptance criteria appropriate for demonstrating that the CMC change or changes will not adversely affect the product.

Line Range	Proposed Text	FDA Draft Text
173-175	We recommend you consider product-specific and process-specific **characteristics** when determining whether to develop a comparability protocol. **Characteristics** can include, but are not limited to, the following: (The use of the word "**attribute**" should be restricted to those "**characteristics**" that may are **inspected** by *sampling* and *examination or classification* to be consistent with the recognized American scientific inspection standard **ANSI Z 1.4**. Similarly, characteristics that are sampled and tested for a level should be called "factors" to be consistent with **ANSI Z 1.9**, the recognized standard governing such inspections.) --- This reviewer recommends the following modifications to the proposed text: 1. Change "characteristics" to "characteristics or factors" 2. Change "Characteristics" to "such" 3. Change "... should be called 'factors' ..." to "... should be called 'variables' ..." The first two changes should be made to improve the accuracy of what is being stated. The third change is needed to correct a mistake by the commenter – **ANSI Z 1.9** addresses the inspection of discrete entities for "variables" or, less precisely, "variable factors," but not for "factors," a term which is the logical union of the terms "attribute" and "variable."	We recommend you consider product-specific and process-specific attributes when determining whether to develop a comparability protocol. Attributes can include, but are not limited to, the following:
190-194	In general, ~~we recommend that~~ a comparability protocol should be considered only if the product resulting from the changes is expected to meet all the requisite CGMP-compliant, approved drug substance, in-process, and/or drug product specifications for each batch and appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for non-routine tests such as characterization studies) to detect and assess the effect, if any, of the change on the approved product. --- Upon review of the text, this reviewer recommends modifying the proposed revision to: "In general, ~~we recommend that~~ a comparability protocol should be considered only if the product resulting from the changesis expected to meet all the requisite **CGMP**-compliant, approved drug substance, in-process, and/or drug product specifications for each batch. ~~and appropriate and sensitive~~ Moreover, scientifically sound and appropriate analytical procedures should have been established and validated or qualified (i.e., for non-routine tests such as characterization studies) to be able to detect and assess the effect, if any, of the change on the ~~approved~~ post-change product."	In general, we recommend that a comparability protocol be considered only if the product resulting from the changes is expected to meet the approved drug substance and/or drug product specifications and appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for nonroutine tests such as characterization studies) to detect the effect of the change on the approved product.

Line Range	Proposed Text	FDA Draft Text
Between lines 232 and 233	**D. When Is a Comparability Protocol Proscribed?** A comparability protocol is proscribed whenever the proposed CMC changes do **not** meet the requirements established in the applicable **CGMP** regulations governing the process or product for which a firm is considering such CMC changes. Thus, before considering any CMC changes, the firm should ensure that said CMC changes collectively, and individually, do not conflict with any applicable **CGMP** requirement.	
255-259	Furthermore, an applicant who is using an approved comparability protocol to implement post-approval CMC changes must assess the effect of the changes on the identity, strength, quality **(including, but not limited to, the batch uniformity of the active or actives in the dosage units and their release from the dosage units)**, purity, and potency of the product as these factors relate to the safety or efficacy of the product prior to distributing product made with the change. (Section 506A(b) of the act.) This reviewer has formalized the suggested the typographical corrections (in a blue font).	Furthermore, an applicant who is using an approved comparability protocol to implement postapproval CMC changes must assess the effect of the changes on the identity, strength, quality, purity, and potency of the product as these factors relate to the safety or efficacy of the product prior to distributing product made with the change. (Section 506A(b) of the act)).
278-281	If you decide to pursue the change, you should submit a prior approval supplement that provides supporting data from a statistically sufficient number of batch-representative units to justify why the change will not adversely affect the identity, strength, quality **(including, but not limited to, the batch uniformity of the active or actives in the dosage units and their release from the dosage units)**, purity, and potency of the specific drug product as these factors relate to the safety and effectiveness of the product. This reviewer recommends changing the phrase "... to the safety and effectiveness ..." to "... to the safety or effectiveness ..." so that the text here is consistent with the corresponding **CGMP** "safety or efficacy" language.	If you decide to pursue the change, you should submit a prior approval supplement that provides the supporting data to justify why the change will not adversely affect the identity, strength, quality, purity, and potency of the specific drug product as these factors relate to the safety and effectiveness of the product.
288-290	We recommend you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the **applicable CGMP requirements**, approved application, and current FDA policy. This reviewer suggests changing "tests" to "sampling plans and tests" to ensure that sampling plans are included in the review process.	We recommend you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the approved application and current FDA policy.

Line Range	Proposed Text	FDA Draft Text
325-328	The comparability protocol can describe a single CMC change or multiple changes. Each change should be specified and the **CGMP-compliant batch-representative inspection plans and batch** acceptance criteria for evaluating the effect of the changes should be well defined. If multiple changes are included in a protocol, we recommend that the multiple changes be interrelated (i.e., one change cannot be made **without the others being made**).	The comparability protocol can describe a single CMC change or multiple changes. Each change should be specified and the acceptance criteria for evaluating the effect of the changes should be well defined. If multiple changes are included in a protocol, we recommend that the multiple changes be interrelated (i.e., one change cannot be made with out the others).
343-352	**2. Specific Sampling Plans, Tests and Studies to Be Performed** A list should be included of the specific **batch-representative sampling plans (e.g., ANSI Z 1.4, ANSI Z 1.9 or ISO 3951, in-house), analytical procedures (e.g., content, release, impurity, appearance), control points (e.g., incoming, in-process, release, post release),** tests (e.g., Assay, pH, Dissolution, LOD, CU) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation) you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g., container closure system) directly affected by the change. Include the ***scientifically sound*** rationale for selecting the particular battery of tests and studies. For example, the use of nonroutine studies (e.g., characterization) can be warranted in cases where in-process or release specifications are not sufficiently discriminatory to evaluate the change. --- This reviewer recommends revising the text and the first-sentence layout to improve accuracy and readability as follows: "A list should be included of the specific: ◆ **batch-representative sampling plans (e.g., ANSI Z 1.4, ANSI Z 1.9 or ISO 3951, in-house),** ◆ **analytical procedures (e.g., content, release, impurity, appearance),** ◆ **control points (e.g., incoming, in-process, release, post release),** ◆ tests (e.g., Assay, pH, Dissolution, LOD, CU) and ◆ studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation) you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, ~~or~~ component (e.g., a different disintegrant level), or packaging system (e.g., new container closure system) directly affected by the change."	**2. Specific Tests and Studies to Be Performed** A list should be included of the specific tests (e.g., release, in-process) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation) you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g., container closure system) directly affected by the change. Include the rationale for selecting the particular battery of tests and studies. For example, the use of nonroutine studies (e.g., characterization) can be warranted in cases where in-process or release specifications are not sufficiently discriminatory to evaluate the change.

Line Range	Proposed Text	FDA Draft Text
356-365	The protocol should specify the number and type (e.g., pilot, production) of population **representative** pre- and post-change batches and/or batch **representative** samples that will be compared. The number and type of batches and/or samples to be compared can vary depending on the extent of the proposed change, type of product or process, and available manufacturing information. However, the numbers chosen must be scientifically sound and representative, and statistically justified. Retained samples of pre-change material can be used for comparison, provided **said samples are batch representative** and there is no significant change in material on storage (e.g., level of degradants increasing over time). A plan would specify whether retained samples are going to be used, and the maximum age of the retained samples, and include information to establish that the samples are **batch representative** and otherwise support the appropriateness of the use of retained samples. In general, the results from the evaluation of a population representative number of post-change material samples should fall within the normal batch-to-batch variation observed for a population representative number of pre-change material samples. --- This reviewer agrees wholeheartedly with the commenter's remarks on the issues raised.	The protocol should specify the number and type (e.g., pilot, production) of pre- and postchange batches and/or samples that will be compared. The number and type of batches and/or samples to be compared can vary depending on the extent of the proposed change, type of product or process, and available manufacturing information. Retained samples of prechange material can be used for comparison, provided there is no significant change in material on storage (e.g., level of degradants increasing over time). A plan would specify whether retained samples are going to be used and the maximum age of the retained samples, and include information to support the appropriateness of the use of retained samples. In general, the results from postchange material should fall within the normal batch-to-batch variation observed for prechange material.
367-376	A comparability protocol should include an inspection plan for the stability studies that will be performed on population representative samples to demonstrate the equivalence of pre- and post-change product. The comparability protocol **should** provide (1) information that **should be** typically provided in a stability protocol, such as the number and type of batches that will be studied, test conditions, and test time points or (2) a reference to the currently approved stability protocol. The amount of stability data that will be generated before the product made with the change is distributed would be specified. The plan for evaluating stability could vary depending on the extent of the proposed change, type of product, and available manufacturing information. **However, the number of representative samples tested must be a scientifically sound, statistically justifiable number.** In some cases, no stability studies may be warranted or a commitment to report results from stability studies in an AR can be sufficient. If no stability studies are planned, we recommend that this be stated clearly **and justified.** --- The word "equivalence" should be replaced with "comparability" because the latter is the proper term to use.	A comparability protocol should include a plan for the stability studies that will be performed to demonstrate the equivalence of pre- and postchange product. The comparability protocol would provide (1) information that is typically provided in a stability protocol, such as the number and type of batches that will be studied, test conditions, and test time points or (2) a reference to the currently approved stability protocol. The amount of stability data that will be generated before the product made with the change is distributed would be specified. The plan for evaluating stability could vary depending on the extent of the proposed change, type of product, and available manufacturing information. In some cases, no stability studies may be warranted or a commitment to report results from stability studies in an AR can be sufficient. If no stability studies are planned, we recommend that this be stated clearly.

Line Range	Proposed Text	FDA Draft Text
378-380	The differences, if any, in the tests and studies from those previously reported in the approved application or subsequent updates (i.e., supplements, annual reports) **must** be described. Because the Draft is guidance, the word "must" must be replaced with "should."	The differences, if any, in the tests and studies from those previously reported in the approved application or subsequent updates (i.e., supplements, annual reports) would be described.
384-400	A protocol should specify the **validated** analytical procedures that you intend to use to assess the effect of the CMC changes on the product or intermediate material. Analytical procedures **with a demonstrated capability to detect new impurities or other changes in a product that can result from the change should** be chosen. Since the current approved analytical procedures are optimized for the approved product and process, modified or new procedures may be warranted. For example, revised or new **validated** analytical procedures may be required to monitor the removal of a new process impurity generated by a new manufacturing process. In this situation, submission of **process-representative** results for pre- and **post-** change products using both the old and new analytical procedures may be warranted. Studies performed to assess the feasibility of the proposed change can often be helpful in determining whether the current approved analytical procedures will be appropriate for assessing the effect of the change on the product (see V.A.5). Validation of new modified analytical procedures or revalidation of existing analytical procedures should be performed, as appropriate. The protocol **should** specify that any new or revised analytical procedures and **their** appropriate validation or revalidation information will be provided whenever a postapproval CMC change, implemented using the approved comparability protocol, is reported to FDA. This reviewer would again recommend that the sentence beginning with "Validation of new modified analytical procedures or revalidation ..." should be revised to ""~~Validation~~ The initial validation of new modified analytical procedures or ~~revalidation~~ the on-going validation or verification of existing analytical procedures should be performed, as appropriate."	A protocol should specify the analytical procedures that you intend to use to assess the effect of the CMC changes on the product or intermediate material. Analytical procedures would be chosen capable of detecting new impurities or other changes in a product that can result from the change. Since the current approved analytical procedures are optimized for the approved product and process, modified or new procedures may be warranted. For example, revised or new analytical procedures can be called for to monitor the removal of a new process impurity generated by a new manufacturing process. In this situation, submission of results for pre- and postchange products using both the old and new analytical procedures may be warranted. Studies performed to assess the feasibility of the proposed change can often be helpful in determining whether the current approved analytical procedures will be appropriate for assessing the effect of the change on the product (see V.A.5). Validation of new modified analytical procedures or revalidation of existing analytical procedures should be performed, as appropriate. The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.

Line Range	Proposed Text	FDA Draft Text
406-414	However, if these analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure **should** be provided **whenever** a post-approval CMC change implemented using the approved comparability protocol is reported to FDA. In cases where changes in analytical procedures are intended to be implemented independent of other CMC changes, we recommend that a comparability protocol specific for analytical procedure changes **should** be submitted (see V.C) To improve reading ease, this reviewer suggests that the first sentence be revised as follows: "~~However, if~~ When these analytical procedures are specified in and provided as part of a comparability protocol and a postapproval CMC change implemented using the approved comparability protocol is reported to **FDA**, the sponsor should provide the following in that report: • ~~any~~ Any new or revised analytical procedures and, • ~~as appropriate,~~ The results and data, if any, from the validation or ~~qualification~~ verification studies for any new or modified procedure"	However, ifthese analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA. In cases where changes in analytical procedures are intended to be implemented independent of other CMC changes, we recommend that a comparability protocol specific for analytical procedure changes be submitted (see V.C)
418-423	4. Acceptance Criteria You should include the ***scientifically sound and appropriate***, **statistics-based** acceptance criteria (numerical limits, ranges or other criteria) **and their scientific justification** for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and post- change material. In general, the drug substance and drug product specification should be **CGMP-compliant** and identical to, or within, the specification limit, range or other criteria contained in the approved application. Any statistical analyses, ***including those required by 21 CFR 211.165(d) for the drug product***, that will be performed and the associated evaluation criteria **should** be identified. [**Note:** If a firm's current approved drug-product application does **not** comply with the requirements set forth in **21 CFR 211**, then that deficiency should be corrected before any other comparability protocol is submitted.] This reviewer suggests that the Agency may wish to modify the text of the "Note"	4. Acceptance Criteria You should include the acceptance criteria (numerical limits, ranges or other criteria) for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and postchange material. In general, the drug substance and drug product specification would be identical to that in the approved application. Any statistical analyses that will be performed and the associated evaluation criteria would be identified.

Line Range	Proposed Text	FDA Draft Text
425-435	If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the **designated** reporting category[3] for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), the change **should** be reported as recommended for the specification change. If the recommended reporting category for the specification change is the same as, or lower than, the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided to the FDA when the post-approval CMC change, **using an approved comparability protocol**, is **implemented and subsequently** reported to FDA. This reviewer agrees with the commenter's changes and with the placing of each sentence in its own paragraph to improve readability.	If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the recommended reporting category[4] for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), the change would be reported as recommended for the specification change. If the recommended reporting category for the specification change is the same or lower than the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.

Line Range	Proposed Text	FDA Draft Text
437-450	**5. Data to Be Reported Under or Included With the Comparability Protocol** You should identify the type (e.g., **in-coming material, in-process material, drug-product acceptance in compliance with 21 CFR 211.165 and, where applicable, 21 CFR 211.167**, long-term or accelerated stability data) and the amount of data (e.g., **"n_i" lot-representative samples of "m_i" incoming lots for "l_i" characteristics, "n_p" representative sample sets from "m_p" process representative evaluations of "k_{pa}" attribute factors and "l_{pv}" variable factors, "n_{dp}" batch-representative sample sets from "m_{dp}" batch evaluations of "k_{dpa}" attribute factors and "l_{dpv}" variable factors of the drug product for acceptance**, 3-months accelerated **process-representative** stability data) that will be submitted at the time a postapproval CMC change implemented using an approved comparability protocol is reported to FDA and, when appropriate, generated prior to your distributing the product made with the change (e.g., when proposed reporting category is a CBE-30, CBE-0, or AR). If available, you may include any **process-representative** data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Data obtained from a *scientifically sound and appropriate* small-scale process or other *scientifically sound and appropriate* studies, incorporating the proposed change, may be used as preliminary evidence that the change is feasible, as well as provide preliminary information on the effect of the change on the product. *Scientifically sound and appropriate* development or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product. --- While this reviewer agrees with what is said, this reviewer thinks that the text layout still needs some improvement. However, this reviewer leaves it up to the Agency to decide how and if the text should be improved.	**5. Data to Be Reported Under or Included With the Comparability Protocol** You should identify the type (e.g., release, long-term or accelerated stability data) and amount of data (e.g., 3-months accelerated stability data) that will be submitted at the time a postapproval CMC change implemented using the approved comparability protocol is reported to FDA and, when appropriate, generated prior to your distributing the product made with the change (e.g., when proposed reporting category is a CBE-30, CBE-0, or AR). If available, you can include any data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Data obtained from a small-scale process or other studies incorporating the proposed change can provide preliminary evidence that the change is feasible, as well as preliminary information on the effect of the change on the product. Development or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product.

Line Range	Proposed Text	FDA Draft Text
462-468	**7. Equivalence Not Demonstrated Using the Approved Comparability Protocol** It is anticipated that some changes in the manufacturing process will result in a postchange drug product that: **a)** cannot be demonstrated to be equivalent to the prechange drug product without more extensive physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or **b)** does not meet the prespecified acceptance criteria in the protocol. You should include in the protocol the explicit steps you will take should either circumstance occur. --- This reviewer again recommends replacing the phrase "... to be equivalent to ..." with the phrase "... to be comparable ..." because "comparable" is the scientifically correct term to use.	7. Equivalence Not Demonstrated Using the Approved Comparability Protocol It is anticipated that some changes in the manufacturing process will result in a postchange product that cannot be demonstrated to be equivalent to the prechange product without more extensive physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or in a product that does not meet the prespecified acceptance criteria in the protocol. You should identify in the protocol the steps you will take in such circumstances.
481-485	**I. Comparison of Physical Characteristics** Acom parability protocol should normally include incoming material and/or in-process material inspection plans that properly compare the physical characteristics (e.g., polymorph forms, particle size distribution, density, flow, affinity) of materials that make up the product produced using the old and new processes when these characteristics are relevant to the safety and the **uniformity** of: **a)** the active or actives, **b)** the release of the active or actives, or **c)** any other key quality factors in the product that can affect its efficacy of the product when taken by the consumer. --- Though the commenter's text is an improvement, this reviewer would propose this alternative: "A drug substance comparability protocol would normally include a plan to properly compare the physical characteristics (e.g., for solids, polymorphs, particlesi ze distribution, bulk and tapped density, flow, permeability, intrinsic solubility; for liquids, viscosity, refractive index, color, density) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product. Similarly, a drug product protocol would normally include a plan to properly compare the physical characteristics (e.g., for solids, hardness, friability; for semisolids, color, density; for suppositories, softening temperature, density; for suspensions, settling time, color, density; for liquids, viscosity, refractive index, color, density, particulates; for solid aerosols, particle size distribution, dose dispersion pattern; and for liquid aerosols, droplet size distribution, dose dispersion pattern) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product."	1. Comparison of Physical Characteristics A comparability protocol would normally include a plan to compare the physical characteristics (e.g., polymorph forms, particle size distribution) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product.

Line Range	Proposed Text	FDA Draft Text
489-502	**2. Comparison of Impurity Profiles** A comparability protocol **should** include a scientifically sound and appropriate inspection plan to determine the impurity profile of the product produced using the new process. The studies would assess product-related impurities and process-related impurities, including, if applicable in-process reagents and catalysts. We recommend that attention be given to demonstrating the absence of any new impurities or contaminants, or that they are removed or inactivated by downstream processing. Any changes in the impurity profile would meet the predefined criteria (see section V.A.4). The predefined criteria should indicate when qualification studies will be conducted to evaluate an increased level of an existing impurity or a new impurity (or an applicant could reference a relevant FDA guidance that recommends qualification levels. Appropriate safety studies should be conducted) unless: **a)** the structure of any new impurity is unequivocally established, **b)** an authentic standard for the impurity is available, **c)** its acute and chronic toxicity and mechanism of action in mammalian species including man is well defined, and **d)** the interaction with the active and other impurities is known to be non-synergistic. If during implementation of a change under an approved comparability protocol, the valid data from the testing of the appropriate process-representative samples indicate that non-clinical or clinical qualification studies for impurities are warranted, the change cannot be implemented under the approved comparability protocol (see III.C and V.A.7). --- This reviewer agrees with the commenter's changes but sees that it would be better if each sentence were its own paragraph.	2. Comparison of Impurity Profiles A comparability protocol would include a plan to determine the impurity profile of the product produced using the new process. The studies would assess product-related impurities and process-related impurities, including, if applicable in-process reagents and catalysts. We recommend that attention be given to demonstrating the absence of any new impurities or contaminants, or that they are removed or inactivated by downstream processing. Any changes in the impurity profile would meet the predefined criteria (see section V.A.4). The predefined criteria would indicate when qualification studies will be warranted to evaluate an increased level of an existing impurity or a new impurity (or an applicant could reference a relevant FDA guidance that recommends qualification levels). If during implementation of a change under an approved comparability protocol, the data indicate that nonclinical or clinical qualification studies for impurities are warranted, the change would not be appropriate for implementation under the approved comparability protocol (see III.C and V.A.7)
513-519	**4. Effect on Process Controls and Controls of Intermediates and/or In-process Materials** We recommend you identify and justify the implementation of any and all: **a)** new controls or **b) deviations** from approved controls. We recommend a statement be included that all of the controls, including those that have been validated to inactivate and remove impurities or contaminants, will be ~~revalidated~~ validated for the new production process, unless an appropriate body of sound scientific evidence clearly establishes that each of said controls are currently operating in the "is valid" state.	4. Effect on Process Controls and Controls of Intermediates and/or In-process Materials We recommend you identify and justify implementation of new controls or variations from approved controls. We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new production process, if appropriate.

Line Range	Proposed Text	FDA Draft Text
521-547	**C. Does FDA Have Specific Concerns About Changes in Analytical Procedures That Should Be Addressed in a Comparability Protocol?** A comparability protocol for changing an analytical procedure **must** provide the plan for validation of the changed analytical procedure and indicate whether the protocol will be used: **a)** to modify the existing analytical procedure (i.e., retaining the same principle), or **b)** to change from one analytical procedure to another (e.g., normal to reverse phase HPLC/UV or from HPLC/UV to GC/FID, or from HPLC to rapid-scan UV/Visible spectroscopy, or from titration to HPLC/UV). The comparability protocol **must** be designed to demonstrate that the proposed changes in the analytical procedures: **a)** improve or **b)** do not significantly affect the critical characteristics (e.g., accuracy, precision, specificity, detection limit, quantitation limit, linearity, and/or **linear** range) [5] used in the validation of methods that are relevant to the type of analytical procedure (e.g., active content evaluation, active release or rate of release, impurity, identity). Method validation should include an assessment of the suitability of the analytical procedure. A validation plan should have *scientifically sound and appropriate* pre-specified acceptance criteria for relevant validation parameters such as precision, range, accuracy, specificity, detection limit, and quantitation limit. The proposed acceptance criteria for these parameters should ensure that the analytical procedure is scientifically sound and appropriate for its intended use. The validation plan should assess whether a revised procedure is more susceptible than the original procedure to matrix effects by process buffers/media, product-related contaminants, or other components present in the material being tested. A plan should identify any statistical analyses that will be performed and **how** the plan intends to use **CGMP**-compliant product testing to compare the two procedures. The need, and plan, for using population-representative product testing to compare the two procedures could vary depending on the extent of the proposed change, type of product, and type of test (e.g., chemical, biological). When used for release or process control, use of the new revised analytical procedure should not result in deletion of a test or relaxation of acceptance criteria that are described in the approved application. [**Note:** The acceptance criteria in the approved application must meet the minimums established in the applicable **CGMP** regulations.] This reviewer supports the commenter's suggestions but, to improve the ease with which the text can be read and understood, he would suggest that each sentence should be its own paragraph.	**C. Does FDA Have Specific Concerns About Changes in Analytical Procedures That ... in a Comparability Protocol?** A comparability protocol for changing an analytical procedure would provide the plan for validation of the changed analytical procedure and indicate whether the protocol will be used to modify the existing analytical procedure (i.e., retaining the same principle), or to change from one analytical procedure to another (e.g., normal to reverse phase HPLC). The comparability protocol would be designed to demonstrate that the proposed changes in the analytical procedures improve or do not significantly change characteristics used in methods validation that are relevant to the type of analytical procedure (e.g., accuracy, precision, specificity, detection limit, quantitation limit, linearity, range).[6] Methods validation includes an assessment of the suitability of the analytical procedure. A validation plan would have prespecified acceptance criteria for relevant validation parameters such as precision, range, accuracy, specificity, detection limit, and quantitation limit. The proposed acceptance criteria for these parameters would ensure that the analytical procedure is appropriate for its intended use. The validation plan would assess whether a revised procedure is more susceptible than the original procedure to matrix effects by process buffers/media, product-related contaminants, or other components present in the dosage form. A plan would identify any statistical analyses that will be performed and whether product testing to compare the two procedures is intended. The need and plan for providing product testing to compare the two procedures could vary depending on the extent of the proposed change, type of product, and type of test (e.g., chemical, biological). When used for release or process control, use of the new revised analytical procedure should not result in deletion of a test or relaxation of acceptance criteria that are described in the approved application.

Line Range	Proposed Text	FDA Draft Text
587-592	**G. Can Implementation of or Changes in Process Analytical Technology (PAT) Be Addressed in a Comparability Protocol?** FDA anticipates that implementation of or changes in PAT could be addressed in a comparability protocol. Early dialogue with FDA is encouraged. The FDA intends to publish **a** guidance on PAT in the future. However, if the PAT intends to change from the quantitative testing of an appropriate population-representative sample set to an approach that uses training sets and the classification of an appropriate set of samples, then: 1. Appropriately rigorous controls will be required for**, and must be implemented for,** all components used in the manufacture of the product. 2. The training sets used to train the classifier will need to appropriately span all of the possible component combinations in sets that are deliberately prepared to address all of the factors (e.g., assay, release, rate of release, impurity) that the classifier is designed to assess. [**Note:** The number of training samples in each training required set should be several times the number of population-representative samples required for the evaluation of the product.] 3. The typical appropriate number of representative samples that need to be classified from a typical batch of product should be based on the attribute number requirements established in ANSI Z 1.4 because classification is an attribute assessment. --- In general, this reviewer supports the text added by the commenter. However, this reviewer suggests the following verbiage modifications: 1. Change the phrase "... if the PAT intends ..." to "... to the extent that the PAT intends ..." 2. Change the phrase "...will be required for**, and must be implemented for,**" to "... should be required for, and should be implemented for," 3. Change the phrase "... classifier will need to appropriately ..." to "... classifier should appropriately..." The preceding changes should be made to align their verbiage with that appropriate in an Agency guidance document.	**A. Can Implementation of or Changes in Process Analytical Technology (PAT) Be Addressed in a Comparability Protocol?** FDA anticipates that implementation of or changes in PAT could be addressed in a comparability protocol. Early dialogue with FDA is encouraged. The FDA intends to publish a guidance on PAT in the future.

Line Range	Proposed Text	FDA Draft Text
594-605	**H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability Protocol?** A master file can be cross-referenced in a comparability protocol that provides for CMC changes (e.g., new manufacturer of drug substance, container resin). The protocol should include a commitment to provide a letter authorizing the FDA to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA. The comparability protocol should also indicate the type of information (e.g., manufacturing and formulation information for a plastic resin) that will be referenced in the master file and the information that you will provide including the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to approved specification, compatibility studies, stability studies). --- This reviewer recommends that the commenter's text be revised to read: "A master file can be cross-referenced in a comparability protocol that provides for CMC changes (e.g., new manufacturer of drug substance, container resin). The protocol should include a commitment from the DMF/VMF holder and, if the holder is located in a foreign jurisdiction, the DMF/VMF holder's authorized representative, to provide a letter authorizing the FDA to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA. The comparability protocol should also indicate the type of information (e.g., manufacturing and formulation information for a plastic resin) that will be referenced in the master file and the information that you will provide including the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to approved specification, compatibility studies, stability studies)."	**H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability Protocol?** A master file can be cross-referenced in a comparability protocol that provides for CMC changes (e.g., new manufacturer of drug substance, container resin). The protocol would include a commitment to provide a letter authorizing the FDA to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA. The comparability protocol would also indicate the type of information (e.g., manufacturing and formulation information for a plastic resin) that will be referenced in the master file and the information that you will provide such as the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to approved specification, compatibility studies, stability studies).

Merck & Co., Inc.'s Submission, Dated June 2, 2003, To Docket 03D-0061: "E-04"

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

These commenters begin by stating, "Merck & Co., Inc, is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R & D) pipeline has produced many of the most important pharmaceutical products on the market, today. FDA, hereafter referred to as *The Agency*, is encouraging industry to use comparability protocols to speed up post-approval changes in lieu of gaining prior approval for these changes. In this new *Draft Guidance for Industry: Comparability Protocols -Chemistry, Manufacturing, and Controls (CMC) Information*, hereafter referred as *The Draft Guidance*. *The Agency* provides recommendations on preparing and using comparability protocols that can be submitted in NDAs and subsequent supplements. Comparability protocols can be submitted for changes to the manufacturing process, analytical procedures, manufacturing equipment, manufacturing facilities, container closure systems and process analytical technology (PAT). Because of Merck's vast experience in this area, we are well qualified and very interested in The Draft Guidance and provide the following comments."

"GENERAL COMMENT

Merck & Co., Inc. strongly supports the development of *The Draft Guideline* and applauds *The Agency* for its efforts. We believe that efficient use of comparability protocols should provide regulatory relief by expediting the review and approval of post-approval changes. This will ultimately bring quality medicines to patients in a timely manner."

"SPECIFIC COMMENTS

Line 97-99 ***A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CM C changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product.***

Comment 1: This statement appears to be incomplete. For added clarity, we recommend that the sentence be modified as follows:

'A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes with potential to have an adverse impact on the identity, strength, quality, purity, and potency of a specific drug product as these relate to the safety and effectiveness of the product.'"

This reviewer disagrees, the purpose of a comparability protocol should be, as written, to assess the effect of the CMC changes on the **"the identity, strength, quality, purity, and potency of a specific ~~drug~~ product as these factors relate to the safety and effectiveness of the product."**

Until proven otherwise, *since all changes may affect the product*, all changes have the potential to adversely, neutrally, or constructively affect the product.

Therefore, added text logically contributes nothing to the clarity of the text.

All that the suggested revision really does is add superfluous verbiage.

However, the text does need to be modified so that it is congruent with the Agency's definition of product in **Footnote 2.**

To provide the needed congruence, this reviewer again suggests the following revision:

"A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes ~~in~~ on the identity, strength, quality, purity, and potency of a specific ~~drug~~ product (in-process material, intermediate, drug substance or drug product) as these factors relate to the safety and effectiveness of the final product."

"Line 152-154 ***With a comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be implemented without an approved comparability protocol.***

Comment 2: The statement appears to be incomplete. We recommend modifying the sentence as follows:

'With a comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, if it were to be reported without an approved comparability protocol.'"

This reviewer would agree that the commenters' alternative is clearer than the Draft's cited text.

However, this reviewer finds that the commenters' proposal fails to address critical aspects of what should be in that comparability protocol.

Therefore, this reviewer would again recommend the Draft's text be changed to read:

"Using the information and data submitted by the manufacturer, the Agency will be able to determine if the proposed changes submitted in a Comparability Protocol will reduce the reporting and/or review requirements vis-à-vis the same changes submitted via an Agency-acceptable filing that lacks a comparability protocol."

"Line 20-24, Footnote 2 ***The general term "product" as used in The Draft Guidance means drug substance, drug product, intermediate, or in-process material, as appropriate.***

and

Line 217-221 ***Specific examples of changes that may be difficult to justify under a comparability protocol can include: A change in the drug substance or drug product specifications.***

and

Line 420-422 ***In general, the drug substance and drug product specification would be identical to that in the approved application.***

Comment 3: The definition of 'product' in footnote 2 of The Draft Guidance makes reference to in-process material. Line 217-221 indicates that it may be difficult to justify a change in drug product specifications under a comparability protocol. Line 420-422 also indicates that, in general, drug product specifications should remain unchanged. We recommend that The Draft Guidance allow for increased flexibility by removing in-process material from the definition of "product." In certain instances a change to an in-process control can be justified, provided that approved finished product specifications are met. When a process change is proposed, a comparability protocol may still be appropriate if there is a change in the in-process controls, as long as finished drug substance and/or drug product specifications continue to be met. For example, a change to the manufacturing process for a tablet should be submitted under a comparability protocol even if the in-process hardness range changes – provided that all release specifications (including dissolution) are met."

This reviewer disagrees with the commenters' proposal because, for discontinuous processes, an in-process material, produced by some step, is the product of that step in the process.

However, a comparability protocol is not appropriate for the product of every process step or, for that matter, every intermediate produced by the process.

To clarify the appropriate usage of the term "product" as it applies to this guidance, this reviewer would recommending the following changes to **Footnote 2**:

"[2] The general term *product* as used in this guidance means drug substance, drug product, intermediate, or in-process material, as appropriate. In general, the use of the term "product" for an intermediate or an in-process material should be restricted to:

a. intermediates and in-process materials that: i) are isolated from the process and ii) may be held for extended periods of time before being reintroduced into the process in a subsequent process step, or
b. intermediates i) purchased from or ii) supplied by a facility other than the facility used to manufacture the final product produced by the process."

Further, this reviewer finds that the text after the commenters' recommendation to remove "in-process material" from the definition of "product" has little to do with the issue raised and, at best, should be completely discounted.

"**Line 255-259** ***Furthermore, an applicant who is using an approved comparability protocol to implement post-approval CMC changes must assess the effect of the changes on the identity, strength, quality, purity, and potency of the product as these factors relate to the safety or efficacy of the product prior to distributing product made with the change.***

Comment 4: The sentence should be deleted as it appears to be unnecessary and does not provide additional information on how a comparability protocol can be submitted. Furthermore, it is redundant with Line 97-99."

This reviewer disagrees.

First, the two cited texts (**Lines 97-99** and **Lines 255-259**) address different issues and, therefore, neither is redundant.

Second, this reviewer finds that the Draft's text is useful.

Third, much of the text in "IV. PROCEDURES FOR COMPARABILITY PROTOCOLS A. How Should a Comparability Protocol Be Submitted?" (**Lines 238-259**) does not provide "how" information (as with the cited text [**Lines 255-259**], most of the other information in the section is also "what" information), but the commenters did not object to that text (**Lines 242-255**).

Based on all of the preceding, this reviewer would, with some modification, again recommend retaining the cited text.

This reviewer suggests the following modified text:

"Furthermore, an applicant who is using an approved comparability protocol to implement post-approval CMC changes must assess the effect of the changes on the identity, strength, quality (including, but not limited to, the batch uniformity of the active or actives and active release [or, for in-process materials, a valid surrogate for said release] for in-process drug-product materials and the drug products and, for drug substances, the key physical properties for intermediates and the "commercial" drug substance), purity, and potency of the product as these factors relate to the safety or efficacy of the product prior to distributing product made with the change. (Section 506A(b) of the act.)"

"**Line 276-278** ***In certain instances, the tests and studies specified in an approved comparability protocol can lead to an unpredicted or unwanted outcome (e.g., test results do not meet predefined acceptance criteria).***

Comment 5: Lines 276-278 indicate that the applicant can elect not to implement the change in an approved comparability protocol. Further guidance is needed on how the applicant can notify *The Agency* of its intent not to proceed with the proposed change in an approved comparability protocol supplement. Should notification to The Agency be made through a written correspondence, Intent to Withdraw letter, Annual Report, etc.?"

"**Line 319** ***V. Content of a Comparability Protocol***

Comment 6: Section V describes the basic elements of a comparability protocol. However, *The Draft Guidance* does not indicate that the applicant should submit a timeline for implementation of the change. The Agency should confirm that once approved, the change described in a comparability protocol could be implemented at the applicant's discretion (with no limit on timing)."

While this reviewer agrees with the commenters' observation about the lack of a timeline,h e does not agree that no limit should be placed on the implementation of an approved comparability protocol.

If firms cannot project when, if ever, an approved comparability protocol will be implemented, the Agency may end up wasting precious review time on comparability protocols that the sponsor has no intention of implementing.

To guard against this waste of Agency resources, this reviewer would propose each approved comparability protocol, like any other "product", should have a defined expiration date.

To guard against implementation delays caused by unforeseeable events, the guidance should provide an expiration extension mechanism to handle such cases.

"**Line 345-349** ***A list should be included of the specific tests (e.g., release, in-process) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation) you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g., container closure system) directly affected by the change.***

Comment 7: We recommend deleting the phrase at the end of the sentence "directly affected by the change," since this is redundant with "effect of the change" in that same sentence."

This reviewer agrees with the commenters' recommendation.

However, to address all areas, this reviewer would recommend changing the text to read:

"A list should be included of the specific tests (e.g., in-coming acceptance for use, in-process material acceptance for use, batch acceptance and release for distribution, stability, investigation of unexpected outcomes) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation, optimization, response-surface mapping, minimum capability) you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g.,c ontainer closure system)~~d irectly affected by the change~~."

"**Line 359-361** ***Retained samples of prechange material can be used for comparison, provided there is no significant change in material on storage (e.g., level of degradants increasing over time).***

Comment 8: We recommend changing the word 'degradants' to 'degradation products.'"

This reviewer does not agree with the commenters' recommendation because the example does not address other critical variable factors that, depending upon the nature of the material, may change over time.

To correct that deficiency, this reviewer suggests revising the text to read:

"**Retained samples of prechange material can be used for comparison, provided there is no significant change in material on storage (~~e.g., level of degradants increasing over time~~** i.e., a measurable change in any controlled physical [e.g., density, flow, segregation of components, morphic form, refractive index] or chemical variable [e.g., moisture, impurity level, degree of oligomerization] which the sponsor has determined to have an adverse impact on the material or its usage in the process)."

"**Line 367-368** ***A comparability protocol should include a plan for the stability studies that will be performed to demonstrate the equivalence of pre- and post-change product.***

Comment 9: The statement indicates that a comparability protocol should include a plan for stability studies to demonstrate the equivalence of pre- and post-change material. We recommend that The Draft Guidance allow for increased flexibility by prefacing the statement with the phrase 'if appropriate,' since some proposed changes may not warrant the performance of stability studies."

While this reviewer agrees with the commenters "some proposed changes may not warrant the performance of stability studies," this reviewer does not agree with the non-specific "if appropriate" prefacing clause.

Because historically seemingly minor process changes have led to unintended stability losses in more than one instance, this reviewer would propose the following:

"Unless the sponsor has and submits documented evidence that no combination of the permissible ranges for the variable factors in thec hanges proposed can adversely affect the stability of the product, a **comparability protocol should include a plan for the stability studies that will be performed to demonstrate the equivalence of pre- and post-change product.**"

"**Line 385-387** ***Analytical procedures would be chosen capable of detecting new impurities or other changes in a product that can result from the change.***

Comment 10: For added clarity, we recommend that the sentence be modified as follows: 'If applicable, analytical procedures should be capable of detecting new impurities or other changes in a product that can result from the change.'"

This reviewer disagrees with the commenters' proposed change for several reasons.

First, as written, the unmodified sentence is not logical.

Second, the proposed modifying phrase "if applicable" is semantically too subjective.

To address both issues, this reviewer recommends the following revision to improve the sentence:

"The analytical procedures chosen should be capable of detecting new impurities or other variable factor changes that may be caused by the changes proposed."

When the sponsor has documented evidence that, for the changes in the process, there are no adverse changes in the variable properties of: a) the defined in-process materials or b) the drug product, including the nature of the impurities present, that evidence establishes compliance with the preceding request.

In all other cases, the documented evidence serves to establish the level of validity required in the Draft.

Therefore, no "exception" or "decision" modifier is needed.

"Line 392-393 ***In this situation, submission of results for pre- and postchange products using both the old and new analytical procedures may be warranted.***

Comment 11: This statement seems to indicate that an assessment should be made using both the old and new methods. We recommend that The Draft Guidance allow for increased flexibility by deleting the references to the use of old and new methods. We recommend modifying the sentence as follows: 'In this situation, submission of results for pre- and postchange products using the analytical procedures suitable for the intended purpose (i.e., monitoring new process impurities) may be warranted.'"

This reviewer disagrees because the text clearly addresses a very real situation – the original (old) method used to test the pre-change product does not resolve the "new" impurity or impurities (discovered in the post-change product using a new method that does resolve said "new" impurity or impurities) from the other components in the pre-change product).

In such cases, in addition to comparing the results from testing the pre-change samples tested using the "old" method to the results from the post-change method using the "new" method, the sponsor should also test the pre-change product with the "new" method and compare the results obtained to a) those obtained when the pre-change product was tested with the "old" method as well as b) those obtained when the post-change was tested with the "new" method.

When the comparisons outlined are made, there are two significant adverse outcomes that may need to be addressed.

The first significant adverse outcome would be finding that the "new" impurity is actually present in the pre-change product and thus not "new" – at a minimum, this may indicate a significant deficiency in the sponsor's existing analytical methodology.

The second significant adverse outcome would be finding that there are significant relative level differences in the "old" impurities between the pre-change samples tested by the "old" method and the pre-change samples tested by the "new" method.

Given the preceding risks, this reviewer can see why the commenters are seeking to change the Draft to eliminate the guidances recommendation for such testing.

However, the preceding possibilities are the reasons that the commenters' proposed change should not be made.

Instead, this reviewer would recommend the following text:

"For example, revised or new analytical procedures can be called for to monitor the removal of a new process impurity generated by a new manufacturing process. In this situation, submission of results for ~~pre-~~ prechange and postchange products using both the old and new analytical procedures may be

warranted. At a minimum, the following comparisons should be made, appropriately reported, and their import determined:

a. *Results* from the testing of the prechange product with the prechange method to the *results* from the testing of the prechange product with the postchange method to prechange product
b. Results from the testing of the prechange product with the postchange method to the results from the testing of the postchange product with the postchange method."

A report summarizing the findings of the comparisons made and stating their import should be issued."

"**Line 406-410** ***However, if these analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure would be provided when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA.***

Comment 12: For added clarity, we recommend that the sentence be modified as follows: 'However, if analytical procedures (new or revised) are specified in and provided as part of a comparability protocol, then the results from validation or qualification of the procedures should be provided when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA.'"

To improve reading ease, this reviewer suggests that the first sentence be revised as follows:

"When: **a) these analytical procedures are specified in and provided as part of a comparability protocol** and **b)** a postapproval CMC change implemented using the approved comparability protocol is reported to FDA, the sponsor should provide the following in that report:

- Any **new or revised analytical procedures and,**
- The **results** and data, if any, **from** the **validation or** verification **studies for any** new or **modified procedure**"

"**Line 506-511** ***We recommend that the effect of the change on downstream processes be examined. Downstream processes such as purification steps can be affected by higher product yields or shifts in impurity profiles when upstream processes are modified. For example, adventitious agent removal or inactivation may have to be reassessed for processes involving materials or reagents derived from a biological source. A comparability protocol would discuss how to ensure that the entire manufacturing process is adequately controlled.***

Comment 13: The discussion on downstream processing appears to contradict a basic premise of BACPAC I which is that impact of changes can be adequately assessed at the first suitably controlled intermediate following the change. We request that **The Agency** addresses this apparent inconsistency."

This reviewer agrees that this Draft and BACPAC Ia re not in agreement here. However, this reviewer would recommend that the reviewer's proposed changes (in the introductory text concerning conflicts between a "current" guidance and a prior guidance) should be used as the Agency's basis for addressing "this apparent inconsistency."

"**Line 517-519** ***We recommend a statement is included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new production process, if appropriate.***

Comment 14: The sentence appears to be incomplete and we recommend that it be modified as follows: 'We recommend a statement be included that controls, including those that have been validated to monitor the inactivation and removal of impurities or contaminants, will be revalidated for the new production process, if appropriate.'"

This reviewer does not agree with the commenters' proposed modification. Instead, this reviewer would recommend changing the Draft to:

"We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be ~~revalidated~~ validated for the new production process~~, if appropriate~~ for both drug substances and drug products to at least the extent required by **CGMP** as set forth in the **21 CFR 211.110**."

"**Line 552-553** ***Comparability protocols may be most useful if applicants are planning to change to equipment with a different operating principal.***

Comment 15: To correct a minor grammatical error, we recommend that the word 'principal' be changed to 'principle.'"

This reviewer agrees with the commenters' recommendation.

FAME System's Draft Submissions To Docket 03D-0061: "E-03" and "E-02"

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

Because the commenter submitted an augmented version of the commenter's drafts as a formal comment ("C-01"), this reviewer did not need to review these two draft responses.

Fine Chemicals Corporation's Submission, Dated February 21, 2003, To Docket 03D-0061: "E-01"

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

This commenter's only comment is:

Section	Comment
1. General Comments	Would it not be appropriate to mention BACPAC I at line 142? This reviewer agrees that BACPAC I is a guidance that should be mentioned in the listing of pertinent guidances

End Of Review Of Comments

To Public Docket 03D-0061,

"Draft Guidance for Industry on Comparability Protocols—Chemistry, Manufacturing and Controls (CMC) Information"