Friday, October 24, 2003

Documents Management Branch [HFA-3051
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Comparability Protocols—Chemistry, Manufacturing, and Controls Information [Docket No. 03D-0061, 68 Federal Register, 8772-8773, February 25, 2003]

To Public Docket: 03D-00061:

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

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contained in the pages that follow, will help the Agency to issue guidance that, in a few instances, the proposed Draft Guidance, fully complies with the **FDC Act**'s requirements for **CGMP** and the requisite adherence thereto that is required of drug product manufacturers with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

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

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

Respectfully,

This Reviewer

03D-0061

EMC 5

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 03D-0061

Introductory Comments

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

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

Time and time, I read some proposed item is a "GMP" issue that need not be included in the Comparability Protocols submitted with respect to Chemistry, Manufacturing and Controls ("CMC") information requested therein because it is a "GMP" issue.

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

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

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

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

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

Moreover, though firms continually point to the **FDA** as the controlling authority over their activities, that Supreme Court decision found that no firm can validly use the **FDA**'s failure to enforce any clear regulatory requirement as a defense in any legal proceeding where the firm has not complied with any clear regulatory requirement.

Because the **CGMP** regulations set forth clear requirement *minimums*, any firm that submits a comparability protocol that does not provide proof that their proposed

systems comply with all of the requirement *minimums* established therein is knowingly submitting a deficient submission.

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

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

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

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

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

REVIEW AND ASSESSMENT OF INDIVIDUAL COMMENTS

Unless a specific science-based, regulation-based, or other issue (for example, a grammatical, spelling or word order error) is raised concerning a given comment in this review of the formal comments to **FDA Docket 03D-0061** (that were available electronically or by other means to this reviewer as of **18 October 2003**), the commenting firm's or individual's comments are, in general, not opposed by this reviewer. [**Note**: The comments, labeled "**C-10,**" from the American Dental Association were not reviewed because they were not available electronically from the Public Dockets Web site.]

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

Following the review of the formal comments, the electronic comments ("**E-nn**") submitted by those that did not provide formal comment are also reviewed.

Active Pharmaceutical Ingredients Committee's (CEFIC/APIC's) Submission, Dated 2 June, 2003, To Public Docket 03D-0061: "C-14"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this 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.]

The commenters begin by stating, "... CEFIC/APIC does not find it useful to comment in detail on this draft Guidance, because the key-problem on the submission of changes by dedicated API manufacturers (DMF holders) should be solved first. Currently DMF holders are completely dependent on their (often many) customers' willingness to submit supplements / comparability protocols for their (A)NDAs in which the DMF is referenced. This willingness is invariably very low."

To a large extent, this reviewer agrees with the commenters' lament on the current status for DMF holders who are not also the manufacturers of the drug products made from their drug substances.

However, the draft Guidance provides the DMF/VMF holder with a means to propose and memorialize their changes both to ensure that the changes proposed are not being proposed to reduce any aspect of the quality of their drug substances and to provide the evidence needed to support the validity of those changes when their next inspection occurs.

Moreover, it does the preceding without adding the burden to either the Agency or the DMF/VMF holder to undergo an approval process that, for processes that the Agency has agreed to treat as "trade secrets," could, as it currently exists, present risks that the "trade secret" status could be irrevocably breached – a highly undesirable outcome.

However, because a DMF/VMF is tied to the accepted site, moving the process from one site to another site: a) revokes the approval status for the product produced at the new site and b) requires the current DMF/VMF holder to file a new DMF/VMF and have one of their customers file a supplement referencing the new DMF/VMF file number to trigger the Agency's review and acceptance mechanisms for the new DMF/VMF file.

As with most things, the preceding is just one of the trade offs that a DMF/VMF holder and the Agency must make to preserve the legal trade-secret status of a DMF or VMF.

Moreover, because products covered by a DMF or VMF are "trade secret" products, the general mechanism by which the DMF/VMF holder notifies its customers is a contractual one between the parties.

This is the case because the Agency is not supposed to disseminate any information concerning the content of a DMF or VMF file because doing so could void the trade secret status of the entire information file.

When notified by the DMF/VMF holder that DMF/VMF holder's process has changed, the drug product manufacturer (the party directly accountable to the public) has the responsibility for addressing the issues of: a) component comparability and b) process change not only internally but, to the extent they change their currently approved or licensed filings, with the Agency.

Since this is the case, it is the drug product manufacturer that bears the direct responsibility for obtaining Agency approval of the drug-product process changes, should any be warranted, that the DMF/VMF holder's change has precipitated.

Thus, when the drug product manufacturer finds that the DMF/VMF holder's changes do not precipitate any change in: a) the approved or licensed manufacturing process for the drug product or b) the drug product manufacturer's filing requirements, there is no need for the drug product manufacturer to file any comparability protocol.

When the FDA next inspects (in an on-site audits) the DMF/VMF holder, the FDA personnel involved then have the responsibility for reviewing the holder's records that justify the accepted site's changes (including any and all personnel, equipment, method, control, SOP, work instruction or other change that the holder has made), if any, that the holder has made since their last inspection.

The commenters continue with, "What the API industry needs is a post-approval change authorization system that will grant authorization to implement the change to the API manufacturer itself instead of to its many customers. Within the current system the use of comparability protocols will almost always be out of reach for the API manufacturing industry sector."

This reviewer does not agree with the commenters' remarks because if what they say is what they want, they can file NDAs or ANDAs for their drug substances and fully disclose their processes.

The choice of filing route has been and still is the choice of the manufacturer of the drug substance (active ingredient or component).

The cumbersome process change mechanisms' burden, imposed by electing to pursue a DMF/VMF filing rather than an NDA, ANDA, NADA or ANADA filing, comes with the "trade secret" advantage that a DMF or VMF filing provides.

These commenters then state, "CEFIC/APIC politely requests further efforts to be taken by FDA to resolve this problem for our industry. Furthermore, we hope for a certain relief in relation to this issue to be obtained from the currently running FDA's CMC Risk Based Review project."

This reviewer would again suggest that the commenters cease looking the proverbial "gift horse in the mouth."

As this reviewer suggests, the DMF/VMF holders should be helping the Agency finalize this draft into a final guidance that the DMF/VMF holders can then use as a template for modeling and memorializing the changes they make to their processes.

Then these holders can use their guidance-compliant comparability protocols and reports (that they would submit in their next annual report) to: **a)** support those changes when they are next inspected and **b)** ensure that their post-change product is comparable to the pre-change product that: **i)** the Agency has "accepted" as being safe and **CGMP** compliant and **ii)** the customers have been receiving.

PhRMA's Submission, Dated July 24, 2003, To Docket 03D-0061: "C-13"

[**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 commenter.]

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

As the commenters say, "The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies ... The comparability protocol represents a potentially useful mechanism to reduce the regulatory burden for sponsors; however, we conclude that its usefulness can be enhanced through the suggestions and revisions detailed in the attachment. In addition, the following general observations highlight major areas where the usefulness of the guidance may be enhanced.

"1. **The scope of a comparability protocol as currently described in the draft guidance is too narrow.**

The guidance suggests that a comparability protocol can describe a single or multiple related changes, but that each change be discrete and specific. If we are to make a significant enhancement to the regulatory process, the scope of the use of comparability protocols must be made wider."

This reviewer finds that the commenters' implicit proposal is that they want protocols to be allowed to be ***non-discrete*** and ***non-specific***!

Moreover, though they state that the proposed guidance "represents a potentially useful mechanism to reduce the regulatory burden for sponsors," they seek a "significant enhancement of the regulatory process" that, as the following will demonstrate, subverts that process.

"Specifically, the protocols should be made applicable to any change in an entire process, such as synthesis or purification of a drug substance or a process change anywhere in the manufacture of a drug product."

This reviewer finds this comment to be disingenuous.

This is the case because the draft text does, "**except for applications for protein products**," address "any change in an entire process" for most drug substances and "a process change anywhere in the manufacture of a drug product" except for protein products.

"The key to allowing use of a comparability protocol in such circumstances is the availability of sufficient manufacturing science data to demonstrate adequate understanding of the substance and product in the light of the proposed changes."

This reviewer could <u>not</u> agree more with what this statement says.

Unfortunately, the reality that this reviewer has seen and that the industry has proposed time and time again (e.g., their recent PQRI 'recommendation' concerning blend uniformity assessment and in-process testing for tablet and related products) is that the industry only talks a good game.

The sampling and test plans that they propose and/or use in that 'recommendation' and elsewhere are <u>not</u> scientifically sound and do <u>not</u> provide "sufficient manufacturing science data."

For example, pharmaceutical manufacturing firms:

1. Improperly use sampling plans that sample one plus the square root of the number of containers for incoming materials,
2. Fail to adequately assess in-process uniformity at each stage of the production of their products for all variables that may adversely affect the requirements established for the product produced,
3. Sample 10's of units from batches where 100's need to be sampled to meet even the minimums needed for 95-% confident decision making (**ANSI Z 1.9** or **ISO 3951**),
4. Use specifications that are not scientifically sound and have no justification beyond they are "compendial specifications that are intended for and are ONLY valid for the product in commerce – not for the release thereof, and/or
5. When they are drug product manufacturers, deliberately ignore the **CGMP** requirement to use statistical process control for batch acceptance (**21 CFR 211.165(d)**).

Thus, these firms fail to provide sufficient data much less the batch- and process- representative data on all factors that may affect the process and/or product.

"Do we understand the critical process parameters and controls necessary to make the substance or product?"

Based on the preceding, the answer is, in most cases, a resounding NO – the industry does not truly understand what the critical process parameters and controls are to reliably manufacture **CGMP**-compliant batches of the drug substance or the drug product.

If they truly did, there would be no recalls for the failure of any of these to meet their post-release ***United States Pharmacopeia*** (***"USP"***) requirements.

As all know, this is not the case.

"Do we understand how robust the substance or product is in the face of changes?"

Based on the failure to collect sufficient data on the original process and the factors that affect it as well as the recalls that continue to occur, the answer is again NO.

"If these data are available, then more comprehensive changes to the manufacture and control of drug substance and drug product should be allowed using a comparability protocol."

Based on this reviewer's knowledge, the preceding statement should have begun with "*If these data were available.*"

This is the case because the manufacturers do not collect sufficient batch representative data at each step in their processes for all variables that may or do affect the control of their processes or the quality of their products for their initial batches much less sufficient data to truly describe their processes (which would require the collection of this data for each variable factor that may affect process control or product quality for 10's to 100's of batches over a significant period of time).

"Furthermore, if such knowledge is available, all changes made under a comparability protocol should be made using an annual report rather than the 'one category lower' proposed in the guidance. (We acknowledge that the guidance indicates a reduction of more than one category is possible 'in some circumstances'.)"

Again, based on this reviewer's knowledge, the preceding statement should have begun with "*If these data were available.*"

The commenters' statement is, for the reasons stated previously, more wishful thinking.

"This would be a more science and risk-based approach, consistent with the integrated quality system being discussed as part of the Quality for the 21st Century initiative."

The preceding comment reminds this reviewer of a song that contains the same refrain "This would be ..."

The commenters' statement sounds good but is lacking in substance and at odds with reality.

"2. **Additional details should be provided about comparability protocols included in an original submission.**

While we agree that comparability protocols may be quite useful in an initial submission, several questions surrounding their use in that manner need to be addressed in the guidance. For example, will their use lengthen the review time? When and how should the reviewer be alerted to the existence of a comparability protocol in an initial submission?"

This reviewer thinks that the CMC Information guidance is the place that the issues raised should be addressed if they have not already been adequately addressed therein.

This guidance is not the place for addressing the issues the commenters raise here.

"3. **The guidance should include a list of examples of changes that might be good candidates for comparability protocols.**

Examples would ensure greater understanding of the entire concept of comparability protocols, as well as identify specific changes for consideration."

This reviewer agrees but would suggest that the industry propose blinded examples and changes that, based on **CGMP** and the companion CMC Information draft guidance, the industry feels should be included in such a list.

"4. **Step down reporting can be enhanced.**

The draft guidance states that a comparability protocol typically allows the reporting of changes one category lower than normally would be the case.

As noted above, we maintain that the guidance should more appropriately emphasize consideration of product/process complexity, robustness and capability in determination of single versus multiple reporting category reductions."

This reviewer does not agree because the key to any reduction should be that the submitting firm must have:

A. A scientifically sound and appropriate body of knowledge including batch representative data for each step in the process that clearly demonstrates

that the firm has studied each variable that may affect the process or the product in its currently approved state,

B. Established adequate monitoring and acceptance controls on each variable, including those for each component used, that has been found to affect the process or the product,

C. Established scientifically sound justifications for each specification that it uses (for incoming acceptance, in-process release and product release) and

D. Collected substantiating process representative data from an appropriate number of appropriate scale batches that establishes that the proposed change does not adversely affect the product – drug substance or drug product – in any manner whatsoever.

Since most firms do not have what they so obviously should with respect to one or more of the preceding, it is difficult for this reviewer to support even the reductions proposed in this guidance much less more than what the draft proposes

"Thus, the overall process should be a major consideration in addition to the changes described in the comparability protocol to help the Agency determine whether a proposed reporting category is appropriate."

This reviewer almost agrees with the commenter's statement – if only they had said, "the *degree of characterization of the* overall process ..."

This is the critical consideration.

IF the firm submits a ***process-representative*** body of data that clearly establishes that the firm truly understands their processes, adequately controls all of the factors that affects that process, produces a **CGMP**-compliant product, and operates in a manner that demonstrates full **CGMP** compliance, THEN the Agency should consider the proposal in light of the current and supporting data, and make an appropriate determination.

"5. The submission, review, and approval of comparability protocols in DMFs require greater clarity.

As DMFs have not been subject to approvals, will the Agency begin treating DMFs (or parts of DMFs) differently?

How will a DMF holder and all authorized users know when a comparability protocol has been reviewed and approved by the Agency?"

Though the preceding questions can only be answered by the Agency, this reviewer would note that the notification of other than the DMF holder is an activity that the Agency should not engage in because this would be a violation of the trade secrete nature of the DMF.

Currently, this matter is a contractual one between the DMF holder and the firms that purchase components from that firm.

"6.If tests and studies approved in a comparability protocol do not meet predefined acceptance criteria, the guidance should allow for reporting categories other than PAS."

In general, this reviewer cannot agree.

Such findings should be and are a clear "red flag" that indicates that the firm submitting the protocol does NOT adequately understand their processes.

As such, these failures should not only trigger the need for a PAS but also trigger **CGMP** compliance concerns because it casts doubt on the body of data supporting the original submission.

"There should be some allowance for discussion with the FDA reviewer to determine if the missed acceptance criteria are of so little consequence that the original proposed reporting category is still appropriate."

This reviewer does not agree.

It should not be left up to reviewers to guess whether or not missing acceptance criteria are of "x" degree of consequence – they do not know the process and cannot, from the limited testing in the protocol studies, know the long-term consequences of the failure to meet submitter's acceptance criteria.

Obviously, the submitters thought the acceptance criteria were important or they would not have set them where they did.

In support of the preceding, this reviewer will offer the following example.

A firm manufacturing a drug substance proposed to change their process by eliminating a filtration step based on the fact that the drug product still met the ***USP*** criteria for that drug substance.

However, to do so, they had to exceed their current acceptance criterion ("< 0.x %") for "salt" in the drug product.

The Agency was convinced to ignore this minor excursion because it was only a small change.

Unfortunately, that small change significantly affected the long-term stability of that drug substance and the drug products made from it increased the level of exposure of the public to the decomposition products generated, lead the firm to ignore "concordance" stability failures and projected failures on the drug substance until the ***USP*** could be persuaded to drop those tests.

The firm was forced to reduce the stability dating period on the drug substances and the drug products made said drug substances from five years to two years.

The result was that the negative impacts of that drug substance on the public were greatly increased and, in some cases, unacceptable batches (as the Agency subsequently detected for a few batches) were used to manufacture drug products that were distributed.

All because of a small change.

From this reviewer's viewpoint, any change that has any observable, reproducible adverse effect, *regardless of its apparent magnitude*, on any of the approved specifications should be rejected.

Changes should improve the quality or, at a minimum, maintain the current level of quality for the drug substance or drug product covered by the protocol.

"Also, allowance should be made for using the reporting category that would normally apply for the change (in the absence of a comparability protocol) in the event it would be less restrictive than PAS."

This reviewer cannot support this illogical statement.

For this reviewer's point of view, all changes in the process, including source of component or raw material, and/or changes to the finished packaged drug product, including vendor source for packaging components, should, at a minimum, require the submission of a suitable comparability protocol.

Having addressed the commenters' general comments, this reviewer will now examine those in the 25 pages of tabulated specific comments that this commenter submitted to the public docket.

Section	Guidance Line	Comment / Observation	Rationale / Justification
General comment		It is important that the definition of comparability be defined in the acceptance criteria of the protocol. This reviewer disagrees; the guidance should simply define the word "comparable" 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." Thus, no process or drug product should bej udged comparable if its produces product that has any safety or other standards or specifications that are materially outside of those in the currently "approved" process or drug product. To be comparable, every aspect (variable factor) of the safety, and the identity, strength, purity and quality of the drug substance and/or drug product produced by the alternative process must be the same or better than that of the currently accepted process. --- An example of a criterion comparing related substances from two processes could be that 'To demonstrate the compatibility of the processes, the total related substance average from process 2 cannot exceed that of process 1 by more than 0.25%' This reviewer finds that the preceding is an example of: 1. A specification that ignores the safety of the drug substance. 2. A widened specification 3. A non-comparability specification	The commenters gave no rationale. Contrary to the commenters' remarks, the definition of comparable should be independent of the acceptance criteria defined in the comparability protocol. To protect the public, the Agency should not approve any protocol that lowers the quality of the drug product below the level established in the original submission that the Agency has accepted as valid based on the studies supporting said criteria. Since today's pharmaceutical industry exists in a world at a time where the accepted general goal of both the manufacturing and the service industries is the continual improvement in quality, the Agency should hold pharmaceutical manufacturers to this minimum standard. Thus, changes that reduce product safety or quality should be unacceptable. Based on the preceding facts, this comment should be ignored. --- The example clearly illustrates the non-valid nature of the commenters' proposal. ***First of all***, a new process is comparable to the accepted one ***if and only if*** the changes do not increase the risk to the patient. ***Second***, a new process is comparable to the accepted one ***if and only if*** the changes do not decrease the purity of a drug substance or the quality of the drug product The reviewer offers this illustrative drug substance example: The change in the level of a trace, but highly toxic, impurity in L-Tryptophan is an excellent example of the non-validity of such. Based on the preceding, the primary criteria for related-substance impurities would be that the acute and short-term chronic toxicities of the related substances should be no greater than those of the current related substances at the maximums allowed in both processes. Secondarily, the sum of the related impurities in the new process does not exceed that of the currently accepted process. In other words, less safe and/or less pure materials are not comparable and processes that generate less safe and/or less pure or lower quality materials should be rejected.

Section	Guidance Line	Comment / Observation	Rationale / Justification
General comment		Part V, B-G should have their own section title (section VI for example) "Specific Protocol Issues." Section V, H & I should also be a separate section (section VII for example) "Additional Issues for Comparability Protocols on Master Files" (for example). This reviewer suggests that the Agency consider the commenters' proposals, but would suggest the last proposed title be changed to "Issues Specific To Comparability Protocols For Materials Controlled By Drug/Veterinary Master Files."	Overall format consistency.
General comment		The usefulness of comparability protocols will be dictated by how easily they fit into overall project timelines. 1. reduced FDA approval timelines for comparability protocol review and comment (rather than 4-6 month current PAS requirement) While this reviewer agrees with the "timely review" sentiment expressed by the commenter, the reviewer would cast **Point 1** in terms of "*reduced **FDA** review timelines for comparability assessment and comment*" and leave it up to the Agency to set timelines based on protocol complexity and length rather than those based on arbitrary dates. 2. inclusion of other FDA groups (Tox/Biopharm) in protocol to assure completeness of FDA response This reviewer agrees and would include Statistics, Manufacturing and Product Quality and the Field Inspectorate as groups that should be involved.	1. In some cases, it will be faster to call the FDA with a specific question, documenting the teleconference, rather than waiting for the approval of a Comparability Protocol in a PAS, and then completing the work and submitting the application (with reduced submission reporting) to FDA Though the reviewer finds the commenters' remark not directly pertinent and interesting, this reviewer would strongly recommend that no **FDA** official engage in such practices – all questions bearing on any aspect of **CGMP** should be submitted in writing (e-mail or FAX) and an appropriately vetted response written response (e-mail, FAX or letter, as appropriate) issued. Since it is inappropriate for an **FDA** employee to give advice that does not conform to the requirements of **CGMP**, the Agency would be better served by a) written requests (by e-mail or FAX), so that what is being requested is clear and b) written response (E-mail, FAX, or letter, as appropriate) since, unlike verbal discussion, it is: i) much more difficult to distort by taking passages out of context and ii) easier to track in existing database structures. 2. Some points such as impurity qualification or dissolution evaluation include FDA groups in addition to CMC reviewers. This reviewer agrees and notes that some changes in equipment, process control point, or inspection plans (sampling, and testing or examination) would benefit from the input from the Field Inspectorate, Manufacturing and Product Quality, and Statistics.

Section	Guidance Line	Comment / Observation	Rationale / Justification
General comment		Section titles constructed as questions seem odd. This construction should be avoided. Providing guidance in the form of "you should" is also odd and uncommon in Agency guidance.	Such headings are inconsistent with the format of other Agency Guidance documents. Shorter section titles would be more beneficial and easier to scan and use.
I	24 footnote 2	Use of the same term "product" to mean anything from drug substance starting material to finished drug product allows for excessive ambiguity in later parts of the Draft. While this reviewer understands the commenters' remark, the reviewer has no problem with the Draft when the term product is used to mean either the drug substance or the drug product. Further, the reviewer found no instance in the guidance where the term "product" could be taken to mean an intermediate or in-process material. For example: • In lines 40-41 and lines 98-99, GMP-type characteristics appear to apply to drug products only; • It is unclear if lines 476-520 refer mainly to biological drug substances or also to the products made from them, and how the SUPAC Guidances (drug product processing) would be applied However to address the commenters' concern, this reviewer proposes to add clarifying text to **Footnote 2** as shown in the adjacent column. ➔	In parts of the Draft in which the FDA recommendations might apply to more than one component, more specific verbiage to specify drug substance, intermediates or drug product should be used. This reviewer leaves it up to the Agency to decide where, if at all, the text needs to be changed in the manner suggested. --- For clarification of **Footnote 2** change that footnote to read: "[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."
I.	32-34	FDA Draft notes that "should" (in the text) indicates an Agency recommendation, rather than a requirement. Please add clarification indicating the wording that will be used for required elements. This reviewer disagrees with the commenters' statements. The requested clarification is inappropriate in a guidance document.	Clarification of required elements "must" vs. "should" vs. "may" Guidance documents do not and should not set requirements. Guidance simply provides the Agency's thinking on one way that the regulated industry can meet the requirements set forth in the FDC Act and the **CGMP** and other applicable regulations regulating the conduct of the pharmaceutical industry.

Section	Guidance Line	Comment / Observation	Rationale / Justification
II.	39-45	Background or Introduction Section needs a glossary to provide the sponsor with a clear definition of regulatory and technical terms used in preparing a comparability protocol. Examples for a glossary are: comparability protocol, comparability report, analytical reference standard, related CMC changes, unrelated CMC changes, drug substance, drug product, isoforms, orthogonal testing, product-specific, process-specific, current protocol, obsolete protocol, qualification or validation lots, PAS, reportable categories, method validation, process validation, FDA review period, criteria for non-comparability, stability-indicating assays. This reviewer agrees with the commenters' suggestion for a glossary but thinks that a key definition that should be included in this Glossary is that of word "*comparable*." This is the case because the goal of a comparability protocol is to show that the output of the postchange process is *comparable* to the output of the prechange process.	Glossary needed
II.	42	Change "(the act)" to "(the Act)" This reviewer agrees but would prefer the use of the common abbreviation "FDC Act" and change "(the act)" to "[FDC Act]."	Typographical correction The use of brackets is typographically preferred over nested parentheses.
II.A.	97-103	Indicate the difference between a comparability protocol (CP) and a validation protocol. This reviewer suggests the obvious, a CP determines whether or not the post-change product is comparable to the pre-change product; a validation protocol establishes that some thing (system, process, method, equipment) performs as it is intended or required to perform. Thus, a CP compares product $A_{i,n}$ to product $A_{i-1,n}$ when process $A_{i,n}$ is known not to be the same as process $A_{i-1,n}$.	Once a CP is approved: a) if the change is small and evaluation is being performed on commercial scale, a validation protocol should not be required, b) if the change is significant and the evaluation is being performed on a small scale batch under the CP, then when the change is implemented on full scale, a validation protocol will be prepared. This reviewer does not understand how the commenters' remarks apply to the request they made in the comments section.

Section	Guidance Line	Comment / Observation	Rationale / Justification
II.A	98	Change "in" to "on". This reviewer agrees but would change the sentence (**Lines 97** through **99**) to read as follows: "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."	Grammatical change The change proposed not only properly broadens the scope of the Comparability Protocol to encompass changes in either a process for a drug substance or one for a drug product but also, by the use of the parenthetical (in-process material, intermediate, drug substance or drug product), defines the general term "product" to encompass in-process materials, intermediates, drug substances and the drug products as those that drafted the text intended.
II.B.	107-109	In footnote 5, clarify how the reduced reporting category is ensured and how the agreement between the agency and the applicant is reached (i.e. discussion). While this reviewer supports the commenters' quest for clarity, this reviewer suggests that, to the degree required, the matters addressed should be addressed in the body of the text	Clarification If the matters raised by the commenters are important, the text of the guidance should address them. If they are not important, then they need not be addressed at all. This reviewer leaves these decisions up to the Agency.
II.B.	109-111	Change from: "Furthermore, because a detailed plan will be provided in the comparability protocol, the FDA is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception)." Change sentence to: "Furthermore, because a detailed plan will be submitted in the comparability protocol, FDA has the opportunity to provide input earlier in the change process and is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception)."	When using a Comparability Protocol, the applicant benefits by receiving FDA's comments regarding the change and assessing the effects of the change earlier in the process than would occur without the use of a Comparability Protocol.
II.B.	110-112	Would the FDA Review Chemist take on a role of distributing comparability protocols that cross FDA disciplines, and providing a consolidated FDA response to the NDA sponsor sooner, or would the sponsor need to send copies for binding comment to other FDA Groups?	CMC elements such as dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Clarification of the administrative process needed to obtain a binding agreement on the Comparability Protocol is requested.
II.B.	112-113	Indicate when validation is performed.	Validation can be performed post-approval of the CP or concurrent with CP approval.

Section	Guidance Line	Comment / Observation	Rationale / Justification
II.B.	109-111	Change from: "Furthermore, because a detailed plan will be provided in the comparability protocol, the FDA is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception)." Change sentence to: "Furthermore, because a detailed plan will be submitted in the comparability protocol, FDA has the opportunity to provide input earlier in the change process and is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception)."	When using a Comparability Protocol, the applicant benefits by receiving FDA's comments regarding the change and assessing the effects of the change earlier in the process than would occur without the use of a Comparability Protocol.
II.B.	110-112	Would the FDA Review Chemist take on a role of distributing comparability protocols that cross FDA disciplines, and providing a consolidated FDA response to the NDA sponsor sooner, or would the sponsor need to send copies for binding comment to other FDA Groups?	CMC elements such as dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Clarification of the administrative process needed to obtain a binding agreement on the Comparability Protocol is requested.
II.B.	112-113	Indicate when validation is performed.	Validation can be performed post-approval of the CP or concurrent with CP approval.

Section	Guidance Line	Comment / Observation	Rationale / Justification
II.D.	127-143	Additional FDA or ICH Guidances addressing dissolution testing, impurity comparisons and bioequivalence should be cited. This reviewer only partly agrees with the commenters' remark. This reviewer concurs with the referencing of other applicable **FDA** guidances but would recommend that this guidance explicitly include/request: **1.** The appropriate sections of the **CGMP** regulations contained in **21 CFR Parts 210** through **226**. **2.** For valid comparisons of drug product units, the minimum inspection plans set forth in **ISO 3951** or its American equivalent **Z 1.9**. **3.** For valid comparisons of drug substances and other non-discrete materials, inspection plans that provide proof that: **a.** The samples sampled and tested are batch representative **b.** The samples sampled are of sufficient size and properly handled in a manner that the sponsor establishes ensures that they are batch representative and each is of sufficient size to provide 10 times the amount needed for all chemical testing or, when physical properties testing is required, five times the size required for all physical tests. **c.** The sample aliquots used for each chemical test are unbiased by the subsampling procedures used and not significantly larger than the size of the dosage unit.	CMC elements such as comparative dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Therefore, other Guidance recommendations concerning "demonstrating equivalence" should be provided. This reviewer is opposed to referencing any ICH guidance that is not been explicitly adopted by the **FDA** and issued as an **FDA** "equivalent." In addition, this reviewer is opposed to any guidance that does not appropriately recognize the requirements of the Federal Food, Drug and Cosmetic Act (**21 U.S.C. Title 9**, the "**FDC Act**"), the current good manufacturing practice ("**CGMP**") regulations in **21 CFR Parts 210** through **226**, and the applicable recognized standards and principles of sound science. The listed items are minimums that should be given to industry to assist them in developing the scientifically sound data sets and "Comparability Protocols" based thereon that these commenters claimed the industry is interested in doing in their general comments. The listed items are also the minimums that should be given to all **FDA** personnel that are involved in any aspect of the **FDA**'s review and inspection processes.
II.D.	143	Add a bullet for BACPAC documents, and a foot note: "BACPAC (Bulk Active Post Approval Changes)"	It applies to this guidance.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.A.	148-150	Change from: "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. Change to: "A comparability protocol *prospectively* specifies how the effect of the 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). While the proposed change is an improvement, this reviewer would propose the following: "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 quality control requirements set forth in **21 CFR 211.165(d).**"	The revised wording makes the meaning of the sentence clearer. While the commenters' revision is an improvement, the reviewer's suggestion changes it to the "should" format suitable for guidance and adds the critical "needs to establish (prove) **CGMP** compliance, including the scientific soundness of the proposed changes." For drug products, the comparability protocol should explicitly include a requirement for demonstrated compliance with **21 CFR 211.165(d).**

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.A.	152-157	Give an example of when a reduction of more than one category is possible. Indicate how the reduced reporting category is ensured. Additional detail should be provided in the guideline to explain how process complexity, robustness and capability are considered in the determination of multiple-level reporting category reductions. In general, this reviewer concurs with the commenters' request for an example. Specifically, a non-complex, robust, capable process should be able to readily utilize multiple level reductions, even for comparability protocols involving several related changes. This reviewer disagrees with the commenters' request because it is filled with terms that the commenters have not defined (e.g., "non-complex," "robust," and "capable" and/or are ambiguous (e.g. "several" and "related"). To address the fuzziness of the commenters' remarks, the reviewer proposes the alternative science-based criteria stated in the adjacent column. Unlike the fuzzy baseline proposed by the commenters for a multiple-level reduction, the reviewer's proposal is a detailed, **CGMP**-compliant, science-based, criteria set that firms that are truly interested in science-based compliance and improving product quality should welcome.	It is not clear how the reduced reporting category is ensured and how the agreement between the agency and the applicant is reached (i.c discussions). While this reviewer would agree that: a) the applicants need to have adequate guidance, b) examples are excellent aids, and c) applicants should have a clear understanding of the acceptance process that the Agency will use, this reviewer is taken aback by the unreasonable demands that attempt to establish nebulous systems as being amenable to multiplel evel reductions. If the commenters want a valid example of a process that might qualify for a single reduction in the level of reporting required, then this reviewer would propose the following as a baseline example. A single level of reduction in the reporting requirements will be considered when: 1. The proposed comparability protocol is based on a existing process that the applicant has established fully complies with **CGMP** including specifically establishing that: **a)** *scientifically sound* and *appropriate* acceptance inspection plans (lot-shipment *representative* sampling, testing, and process-appropriate physical and chemical property specifications) are used for all incoming materials, **b)** batch- or lot-*representative inspection plans* are used for each phase (step) in the process and the plans cover/monitors any and all variables that may affect the process or any aspect of the safety or quality of the product, **c)** the release inspection process includes *batch- or lot- representative-sample* inspection plans for all controlled variable factors, that, at a minimum, are based on ***ISO 3951:1989*** or ***ANSI/ASQ Z 1.9*** and use statistical quality control (**SQC**) for the drug product or, for drug substances, batch- or lot- *representative samples* are tested for all critical material variables including the principal physical properties, and **d)** the effect of changes in the variable factors on the process are well defined; 2. The changes proposed for the revised process fully comply with **CGMP** and are projected to produce a product that is no less safe or pure than the existing or basis process; and 3. The change or changes are confined to one phase or step in the process or, if changes in more than one step or phase in the process are proposed, these have been proven to be unrelated and uncorrelated (orthogonal) by the proper application of the appropriate statistical procedures on batch representative data sets for each change being proposed.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.A.	154-156	Change from: "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)." Change 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)."	The current example is confusing. Going from a PAS to an AR would normally be considered a three-category reduction.
III.B.	163	CMC changes do not have to be "related" to qualify for comparability protocol. This reviewer believes that the decision as to whether or not unrelated CMC changes qualify for a comparability protocol rests with the Agency. As the guidance stands, the changes do have to be related. Furthermore, if unrelated changes were to be permitted in a single comparability protocol, then the applicant should be required to prove that the unrelated changes were orthogonal. Below are examples of unrelated manufacturing changes that could occur at different steps in a process but would still qualify for submitting a comparability protocol: ◆ Change in vendor supplying the same starting material ◆ Modified a component(s) for milling equipment ◆ Changed hold time between two steps of a purification process ◆ Used new improved resin for a chromatography step ◆ Used a low extractable polymer for container/closure system component This reviewer finds the commenters' examples, though grammatically deficient, are examples, except for the last example, of changes that could be unrelated but may be related.	CMC changes do not have to be "related' to qualify for a comparability protocol. The commenters' rationale simply restates their comment without providing any reasoning for their assertion. While each example could qualify for 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. Moreover, seemingly unrelated changes may, in fact, be related. For example, the change in the vendor supplying a starting material may result in the substitution of a material that has the same chemical properties but a different particle size and/or different crystal form that may require a change in the screen used to mill that raw material. Or, a change in the source of a raw material may introduce or remove an impurity that affects the crystallization rate in the process necessitating an increase in the hold time for crystallization completion. Or the change in raw material may require a change in the resin used for a chromatography step to remove a new undesirable impurity. Therefore, if the Agency does decide to allow "unrelated" changes, the guidance provided should require the applicant to prove that the changes are truly orthogonal – non-interacting before accepting them as "unrelated" simply because they are in different steps and the relationship between them is not obvious.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.B. (Cont.)	163 (Continued)	Comment/Observation (Continued) A comparability report would have to demonstrate that the sum of the unrelated process changes had no adverse effect on the identity, strength, quality, purity or potency of the drug product. Results would be compared to established specifications for the analytical reference standard used to release drug substance or drug product produced <u>without</u> the change. This reviewer finds the commenters' remarks, at best, incomplete. The reviewer would suggest that the preceding be rephrased to read: "*Based on the results obtained from the testing of a statistically valid number of batch representative samples produced under both the worst-case conditions and nominal-case conditions allowed in the proposed changes*, a comparability report should have to establish (prove) that the sum of the proposed process changes (related and unrelated) had no adverse effect on the **safety**, and the identity, strength or potency, quality (including impurities, physical properties, performance variables and stability), and purity of the drug substance or the drug product. The batch-representative results obtained and their projected population values from all safety and other testing on the changed process should be no less than the established **CGMP**-compliant (scientifically sound, appropriate and batch representative) in-coming-, in-process- and product- acceptance specifications for the for the drug substance or drug product produced <u>without</u> the change. Sufficient batches should be evaluated to establish, *at a confidence level of 95 % or higher*, that the changes have had no adverse impact on the process or, more importantly, the product produced. In cases where the applicant wishes to minimize the number of batches required to establish process 'comparability,' then a multiple of the minimum number required for the batch can be used to compensate for the reduced number of batches. However, not less than two (2) batches at the nominal change levels and one at the worst-case levels should be evaluated."	Rationale/Justification (Continued) The first problem this reviewer finds is that the issue of product safety is again overlooked. This omission is especially egregious for changes in processes that produce bulk drug substances. In addition, the commenters fail to address **CGMP**-compliance in the areas that are critical to establishing (proving) that batches produced by different processes are truly comparable – not just that the samples tested give comparable result values. To do what **CGMP** requires, sufficient batch-representative samples must be sampled and tested at the completion of each phase and for acceptance of the batch for release to project, *using the appropriate statistical procedures at a confidence level of 95 % or higher*, that the batches meet the same specifications as the *scientifically sound, appropriate* specifications established for the baseline (unchanged process) batches– not just that the samples tested gave comparable results. Only when the preceding constraints are satisfied for a sufficient number of batches (and, unless the change is for a single variable, three (3) batches are not enough <u>unless</u> nominal and worst-case change levels show that the changes have no adverse effect on the process or the drug product) can one validly assert that the effect of the proposed changes has had not adverse effect on the process and/or the drug substance or drug product. Thus, as the complexity of the process and the changes proposed increases, the minimum number batches required to establish "no adverse impact should also be increased. For the ubiquitous "3 batch" drug-product case, the number of dosage units evaluated for each variable factor (tracked by the ***USP*** post-release) from each batch should be not less than twice (2 times) the number established in **ISO 3951:1989** (or **ANSI/ASQ Z 1.9**) for the normal-inspection-level, process-variability-unknown case Should the firm wish to estimate process capability, they should follow an approach like the minimum capability approach published in two parts in ***Pharmaceutical Engineering*** in late 1999 and early 2000

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.B.	163-164	Change from: "However, we recommend that each change be discrete and specific." Change to: "The use of the Comparability Protocol for technology specific changes (e.g., change in filtration process) that broadly apply to multiple products is also appropriate. Process complexity, robustness and capability may help determine the appropriateness of including multiple related changes in a comparability protocol. This reviewer cannot agree with the changes that the commenters are proposing because, *regardless of the number of changes*, each change should, as the draft text states, **"be discrete and specific."** In addition, the commenters' remarks are not even self-consistent. The first talks of technology specific changes applied to multiple products while the second speaks to multiple related changes in a comparability protocol. Changing the example filtration process to a different filtration process might affect different processes differently and, for that reason, should not be proposed in a blanket protocol, as the commenters would suggest. Moreover, the commenters' example did not even suggest that such be limited to cases where the proposed filtration process change is known to improve the quality of the desired fraction (filtrate or filter cake).	Wording should be broadened to allow technology-specific multiple-product changes (e.g., new bottle for several oral solids). The commenter's rationale simply restates the first sentence in the proposed change. Moreover, the need for each change to be discrete and specific is obvious. A proposed change should not change a pH limit from 'not more than 4.0' to 'not more than 3.5 to 4.5.' – a limit should be a discrete number. Similarly, one should not propose changing a process that states 'add 200 L of 1 N aqueous acetic acid' to one that says 'add 200 L of a suitable 1 N acid solution' – a change should be specific. With respect to "technology specific changes," let us consider the two examples, the one in the commenter's "Comment" column and the other in their "Rationale" column. Obviously, changing a filtration process to a new one that improves the "quality" of the filtrate containing the active in Process "A" could adversely impact the "quality" of the filter cake containing the active in Process "B" The second example, "new bottle for several oral solids," is more of an item change than a technology change. However, the same caveats apply in that the protective effect of the new bottle may not be the same for all of the different oral solid products. Moreover, though current technology exists to make plastic bottles impervious to the diffusion of deleterious gases (such as water vapor, oxygen, carbon monoxide and dioxide, and nitrous and nitric oxides) and light, few firm seem willing to adopt such bottles preferring to use overwraps and adsorbents to control the problems. Most "new bottles" are attempts to use cheaper bottles not better bottles. Also, the guidance should describe situations where multiple related changes are appropriate for a comparability protocol. This reviewer again would leave it up to the **FDA** to describe the **CGMP**-compliant situations where such are appropriate.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.B.	168-170	This line implies that the purpose of the acceptance criteria is to demonstrate that no adverse effect has occurred as a result of the change. However, Section II D line 134 implies that the purpose of the acceptance criteria would be to demonstrate equivalence. Demonstrating equivalence and demonstrating no adverse effect are not the same. While this reviewer finds the commenters' remarks have some merit, the key is, as they indicate, in the definition. This reviewer again recommends that the draft guidance appropriately define the term comparable as, "**Comparable:** For the purposes of this guidance, alternative processes and products produced by alternative processes are deemed "comparable" to the original Agency-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." Thus, **CGMP**-compliant processes that produce in-process and finished products having the same or increased safety, identity, strength or potency, quality and purity when compared to the in-process and finished products produced by the original **FDA**-accepted **CGMP**-compliant process are "comparable." Those processes that produce products that have decreased safety, identity, strength or potency, quality and purity when compared to the in-process and finished products produced by the original **FDA**-accepted **CGMP**-compliant process are "non-comparable." A **CGMP**-compliant process that generates comparable products is comparable to a process that generates products that have no adverse effects vis-à-vis the products produced by the original **FDA**-accepted **CGMP**-compliant process.	The definition of an Adverse Effect is a key element, which should be stated in the protocol. This reviewer disagrees, the definition of an adverse effect is independent of the protocol – any process effect that reduces the safety, identity, strength or potency, quality and purity of the products produced vis-à-vis the original **FDA**-accepted, **CGMP**-compliant process is an adverse effect. Thus, finding an adverse effect is equivalent to finding that the processes are non-comparable. Based on the preceding, the text in the draft should be changed as follows: 1. **Lines 42-44** should be changed to state: "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~~ comparable (**see Glossary**)." 2. **Lines 127-128** should be changed to read: "D. Where Can More Information on Postapproval Changes and Demonstration of ~~Equivalence~~ **Comparability** Be Found?" 3. **Lines 133-135** should be changed to read: "The following guidances provide especially relevant information on (1) demonstrating ~~equivalence~~ comparability, (2) documentation to be provided to support postapproval changes, and (3) the recommended reporting categories." 4. **Lines 367-368** should be changed to state: "A comparability protocol should include a plan for the stability studies that will be performed to demonstrate the ~~equivalence~~ comparability of pre- and postchange product." 5. **Lines 418-420** should be changed to state: "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~~ comparability between pre- and postchange material." 6. Lines 462-467 should be changed to state: "7 ~~Equivalence~~ **Comparability** 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~~ 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 acceptance criteria in the protocol."

Section	Guidance Line	Comment / Observation	Rationale / Justification
		Comment/Observation (Continued) Thus, a proposed process is comparable to the original process if and only if it is **CGMP** compliant and yields **CGMP**-compliant products that have no adverse effect vis-à-vis the **CGMP**-complaint products produced by the original **FDA**-accepted **CGMP**-compliant process. Corollaries are: ◆ All products and processes must be fully **CGMP**-compliant or the product produced is, by law, adulterated and cannot legally even be offered for sale. ◆ To ensure that there is no loss of the improved level of safety, identity, strength or potency, quality and purity over the change history of the manufacture of a given product, all comparability protocols should compare each proposed "changed" process to that validated **FDA**-accepted **CGMP**-compliant process which produces product that has the highest level of safety, identity, strength or potency, quality and purity.	Rationale/Justification (Continued) A significant change in the production process doesn't have to mean that the product is affected adversely. Is the definition of adverse effect that there could be a change in the product's characteristics so that the patient health is at risk? As this reviewer has defined it, an adverse effect is any effect that renders the product produced non-comparable to the product produced by the current **FDA**-accepted **CGMP**-compliant process with respect to safety, identity, strength or potency, quality and purity. Or is the change, per se, an adverse effect? First, a change cannot be an effect – only the result of the change can be an effect, favorable, neutral or adverse. Since the result of a change can and, in some cases does, lead to an improvement in the level of safety, and/or the level of identity, strength or potency, quality and purity vis-à-vis the current **FDA**-accepted, **CGMP**-compliant product produced by the **FDA**-accepted, **CGMP**-compliant process, the results of changes cannot be, per se, adverse effects.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.B & C.	183 and 211-213	The Draft appears to be stating that a change in impurities requiring safety evaluation might or might not be amenable to a CMC Comparability Protocol. We request clarification. This reviewer agrees with the commenters that the two statements appear to be at odds with each other. However, in the context stated there is no conflict. **Line 183** simply lists one factor," **The effect on safety of changes in the impurities,**" that the applicant should consider when deciding to develop a comparability protocol. **Lines 211** through **213** state a "general" impediment, "**A CMC change that requires efficacy, safety (clinical or nonclinical) studies, or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities),**" that the Agency sees to using the comparability protocol approach. However, **Lines 215** through **217**, provide the possibility for the sponsor to overcome the impediment when it states, "**It may be possible to design a comparability protocol for some of these CMC changes, but FDA may be limited in its ability to designate a reporting category other than PAS for changes implemented under such a protocol.**" However, since this reviewer knows that safety must be an overriding consideration in all cases, this reviewer would change **Line 183** to "**The effect on safety of changes ~~in the impurities~~**" and **Lines 211** through **213** to read: "**A CMC change that requires efficacy, safety (clinical or nonclinical) studies** needed for new impurities, or **PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities).**" The preceding change is needed to permit comparability protocols when the change only affects the level of the existing known impurities but, in general, proscribe this approach when any new impurity emerges.	The two passages seem contradictory. The commenters' remark is correct, when taken out of their contexts, the two passages seem to be contradictory. In their contexts, the passages cited by the commenters are obviously non-contradictory. However, to ensure that all comparability protocols explicitly consider safety, this reviewer would recommend removing the "**in the impurities**" restriction from **Line 183**. In addition, this reviewer would restrict comparability protocols to only when no new impurities are found provided the appropriate acute and short-term chronic non-clinical toxicity studies are included whenever the level of one or more impurities increase even in cases where the total level does NOT change. In this reviewer's experience, the only time that such toxicity studies would be superfluous would be the case that the change introduces no new impurities and/or reduces the level of all of the existing impurities. Thus, a truly improved, not simply changed, crystallization process that reduced all impurities or the addition of a recrystallization step that significantly reduces all impurities without introducing new ones would be drug substance examples where no extensive safety tests would need to be included in the protocol. However, a sponsor may want to include a simple toxicity evaluation to assess the level of improvement in the process. Finally, this reviewer would again recommend that the Agency consider including a specific bar to the use of a comparability protocol approach unless the sponsor has established that the current process and product is fully **CGMP** compliant, the sponsor has **CGMP**-compliant data that substantiates the probable non-deleterious effect of the proposed changes, and the proposed changed process has been proven to be fully compliant. Thus, a comparability protocol that proposed to drop a **CGMP**-mandated in-process control should be proscribed. However, one that proposed to change the test or reduce the number of samples from that required in the current **FDA**-accepted **CGMP**-compliant process to a lesser, but still **CGMP**-compliant number, should be considered.

Section	Guidance Line	Comment / Observation	Rationale / Justification
III.B.	190-194	We recommend Lines 190-194 of the text be moved from the end of the section to the beginning of this section, so that it appears more prominently to the reader.	Proposed will emphasize that comparability protocols should only be considered when changes associated with product-specific and/or process-specific attributes are well known, capable of being detected with established, validated or qualified, analytical procedures, and expected to meet previously approved specifications.
III.C.2	27	Add "For the API" at the beginning of the sentence. In the context in which this line is stated, this reviewer disagrees with the comment and supports leaving the text as it stands.	Such a change of excipients should be possible in a comparability protocol. (e.g., switch from animal-based magnesium stearate to vegetable based magnesium stearate) First of all, the commenter's example is not relevant to the text because, unlike the text in **Line 227**, "A change from synthesis-derived to naturally sourced material and vice versa," the example is a change from one naturally derived source (animal) to another naturally derived source (plant). Given the differences in not only the impurity profiles but also the physical properties of synthesis-derived materials vis-à-vis naturally-sourced materials, the Agency should keep the draft text as it is for both safety and process performance considerations, and, for the drug product, dosage performance considerations.
III.C.224-	226	Change the bullet to include the underlined text: "A change from plant, animal, or multicellular (e.g., algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal), depending on the extent of the purification process. In context, this reviewer again opposes adding the commenters' phrase.	If the downstream purification process is extensive it should be possible to handle such a change under a comparability protocol. In the context in which this text appears, the modifying clause is not only superfluous but also introduces unneeded ambiguity. The bullets are "Specific examples of changes that may be difficult to justify under a comparability protocol can include." Therefore, this bullet does not warrant the "it depends" ambiguity that the commenters are seeking to introduce.
III.C.227		Change the bullet to include underlined text: "A change from synthesis-derived to naturally sourced material and vice versa, depending on the extent of the purification process" In context, this reviewer again opposes adding the commenter's phrase This reviewer also notes that the commenters apparently made a conscious decision to separate the two changes they were seeking to make to **Line 227** and would recommend that the Agency seek to find the reason for the separation.	If the downstream purification process is extensive it should be possible to handle such a change under a comparability protocol. In the context in which this text appears, the modifying clause is not only superfluous but also introduces unneeded ambiguity. The bullets are "Specific examples of changes that may be difficult to justify under a comparability protocol can include." Therefore, this bullet does not warrant the "it depends" ambiguity that the commenters are seeking to introduce.

Section	Guidance	Comment / Observation	Rationale / Justification

	Line		
III.C.229-	231	Delete lines 229 – 231 and insert the following new paragraph: "When a Manufacturer moves a process to a previously uninspected manufacturing facility, the approval of the Comparability Protocol signifies that the Manufacturer should notify the field that the facility is now ready for inspection status. The inspection should be scheduled prior to the submission of the agreed data package to the review division. Upon receipt of the acceptable GMP status, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol." In context, this reviewer again opposes making the commenter's suggested changes. Moreover, the proposed paragraph speaks of conditions that may be contrary to reality, "the approval of the Comparability Protocol" and what this approval "signifies." The commenters' proposed text ignores the reality that the protocol may be rejected and, in such cases, the existence of a submitted Comparability Protocol is of no significance. Further, the commenters', "Upon receipt of the acceptable GMP status, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol," misidentifies the standard required of the facility as "acceptable GMP status" when the **FDC Act** and the **CGMP** regulations require the site to be found to be "fully **CGMP** compliant" before any product may be even offered for sale.	Since both a Comparability Protocol and a change to a site which requires a cGMP inspection must be submitted as a Prior Approval Supplement, why would it not be appropriate for the Comparability Protocol to be used as the trigger for the cGMP inspection? Then, after the PAI and Comparability Protocol approval, the site change could be reported at the reduced reporting category. Though commenters phrase the question so elegantly, they attempt to confuse the realities that they pose as a question. If, as they initially state, a Comparability Protocol would in this case require a PAS, then why do they state, in their second remark, "the site change could be reported at the reduced reporting category" when, if their initial statement is true, their second statement is, at best, illogical. Moreover, their attempt to use the false logic that "if A requires C and B requires C, then A and B are a priori equivalent." Finally, they fail to answer their own question – the obvious answer is that the Agency sees that such approaches should not be allowed. Moreover, the text does allow for the possibility that such a Comparability Protocol may be allowed in some cases (**Lines 217** and **218**, "Specific examples of changes that may be difficult to justify under a comparability protocol can include." Further, in the context in which this text appears, the text should be kept as it is and the proposed paragraph has no place. The bullets are "Specific examples of changes that may be difficult to justify under a comparability protocol can include." Therefore, the proposed changes are both unwarranted and misplaced.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.A.	238-252	Where is the comparability protocol (and report placed within the structure of the CTD? Would comparability protocols (CP) be placed as region-specific templates in the specific sections under which they directly apply, (i.e. if a CP is for a drug product manufacturing process change, the template would be placed under CTD section 3.2.P.3.3 Description of the Mfg Process)? If that is the case, what would be recommended for those CPs that support multiple changes?	The commenters provided no rationale.
IV.A.	238-240	The Draft notes that the cover letter for the application should state that a comparability protocol is in the submission, to properly direct review. It is unclear whether this is also the case for original NDA letters, which typically don't get into the specifics of what documentation is in the submission.	The administrative process and cover letter annotation for original NDAs needs clarification.
IV.A.	244-245	Indicate why a CP can not be submitted as a CBE or CBE-30. The answer from this reviewer is that CPs need careful Agency review of the requisite supporting data provided or referenced to ensure that the proposed CPs are fully **CGMP**-compliant. To permit this, the Agency has rightly classified a CP as a PAS and properly treats it as such. Why not make the submission format consistent with the nature of the change as specified in FDA guidances rather than making all protocol submissions PAS. The answer to the commenters' question is obvious, a CP is not a change, it is a protocol submitted in support of a proposed change that itself requires different levels of notice IF the protocol is accepted by the Agency.	The bullet indicates that a CP itself is always in a PAS. A CP is supposed to propose changes that the sponsor has an appropriately large body of submitted documented supporting evidence that establishes that the proposed changes: **a)** Will, if implemented, produce comparable product where the definition of "comparable" is the same or better and **b)** Are themselves and the products produced are fully **CGMP** compliant. It seems to this reviewer that the commenters' remarks are deliberately obtuse and intended to promulgate a position that deliberately confuses a protocol in support of a proposed change with a document submission requirement for the change itself. Moreover, the commenters' remarks are presumptuous, at best, because they fail to address the case where the Agency rejects the CP because it either proposes changes that: a. Do not comply with **CGMP** or b. Are <u>not</u> adequately justified by the body of supporting data submitted as evidence that the changes will produce ***comparable*** product.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.A. (Cont.)	244-245 (Continued)	Comment/Observation (Continued) There needs to be clarity on how long FDA will take to review a comparability protocol. When submitted as a PAS the implication is the review is up to 180 days like a PAS for all protocols. Based on the commenters' remarks it is clear that the commenters understand how long the **FDA** may take for a CP and need no further "clarity" on this issue. The intent of the protocol is to obtain consensus with FDA on documentation required to support the change and the filing strategy/plan. In essence protocols are submissions without data and should track with the categories already defined in FDA guidance documents. Again, the commenters attempt to assign their own view of what the intent should be instead of what the intents of the CP should be and, in fact, are. The most egregious statement made by the commenters is their assertion that "protocols are submissions without data" when, in fact, they are supposed to be submissions of proposed changes supported by a body of information and data. Based on all of the preceding realities, this reviewer would recommend that the comments made here be disregarded.	Rationale/Justification (Continued) The Draft clearly and properly classifies a CP as a PAS. As such, the timelines are clear and no additional clarification is needed. Given the name assigned by the Agency, "Comparability Protocol," it is or should be obvious that the Agency is providing a mechanism by which a manufacturer can have the validity of a proposed change determined by the Agency. To obtain **FDA** acceptance, the CP must provide a detailed description of the change and its projected effects, if any, and the body of evidence that establishes that the proposed changes, if implemented, are predicted to produce comparable (the same or better) product and are fully **CGMP** compliant. Thus, the commenters' statement characterizing comparability protocols as "submissions without data" is patently false on its face. The text should remain as it is.
IV.A.	246-250	Re-write to indicate that the PAS "can" include the CP. This reviewer finds no need for the suggested rewrite. This is the case because, in the context stated (**Line 242, "The submission can consist of the proposed comparability protocol in"**), the draft is clear as written.	The way it is stated may lead to an expectation that a protocol also needs to be submitted together with a proposed change which is contrary to the intent that the CP is optional (line 103). This reviewer is surprised that the commenters have again obviously failed to read the statements made in their proper context. However, even if a PAS does not contain a CP is should contain a body of facts and data that substantiate what is proposed is **CGMP** compliant and will, if accepted by the Agency and implemented by the sponsor, result in product that is the same or better than the currently accepted, approved or licensed product.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.A.	251-252	This is the best way for a CP to be submitted to result in time saving when performing the change.	If the CP is submitted by itself as a PAS, the only benefit would be if the data can be generated in parallel with the approval process, and the change implemented as soon as the CP is approved. The commenters' rationale is again flawed and again overlooks a) the reality that a CP may be rejected by the Agency as well as b) the post-change submission requirements that the sponsor must adhere to. Moreover, there is no prohibition to the sponsor's collecting the data from post-change batches before the CP submission is made as should be the case if the CP is submitted as an original "CMC" application (governed by the Agency's current "CMC Information" guidance).
IV.A.	254-259	Guidance states that the protocol must be approved prior to implementing the change. Protocol review times are not defined or described. The commenters' first remark states the obvious. The commenters' second remark is also accurate but irrelevant. The commenters' rationale remarks are observations presented without any supporting facts and, in general, are, at best, peripheral to the observations made. Based on the preceding, these remarks should be ignored.	If the reviews are more than 30-45 days, the sponsor will lose a lot of time (i.e. getting stability studies started early) on making the change. This reviewer again finds it odd that the commenters are making observations that have little to do with the text in question. Since the review timelines are properly stated as those for PAS, nothing more needs to be said. If the sponsors' overriding concern is the potential time of the review, then the sponsors should do all in their power to see to it that: a) their CPs are for changes that are comparable, and b) the supporting body of evidence clearly establishes that the changes proposed are **CGMP** compliant and will, if implemented, produce product that is the same as or better than the product produced by the **CGMP**-compliant baseline process. Moreover, except for the cost, there is nothing that prevents a firm from making the change for a few batches and proving that the changes do, in fact, produce comparable product prior to the submission of a CP as the guidance clearly indicates in **Lines 246** through **250**. Comparability protocol review should be less that the agency review for post-approval supplements; otherwise it defeats the purpose for a reduction in reporting category. For all of the reasons stated previously, this reviewer knows that this remark has no validity. Moreover, other than their words, the commenters provide no supporting facts for their statements.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.A.	254-259	This paragraph suggests that product made under the change can be distributed after the assessment. The paragraph should also contain the following information. "The applicant must assess the effect of the changes ... and submit the changes in accord with the reporting category designated in the approved protocol prior to distribution ..." While the heading in **Line 236**, "A. How Should a Comparability Protocol Be Submitted?", indicates that the section only addresses submission issues and the heading of the next section in **Lines 261** and **262**, "B. How Are Changes and Study Results Submitted After a Comparability Protocol is Approved?", indicates that this section is where the commenters' inferred concerns are addressed, this reviewer would agree that the last sentence, "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))," needs to be revised but would suggest that the clause, "prior to distributing product made with the change. (Section 506A(b) of the act)," should be moved to the next section and a sentence added that states: "The following sections ("**IV. B.**" and "**IV. C.**") address what a sponsor should then do with regard to submitting the results of the sponsor's assessment and proceeding beyond the assessment." In addition, this reviewer suggests that the title of **IV.A.** should be changed to: "How Should a Comparability Protocol Be Submitted And, If Approved, The Results of the Changes Be Evaluated?"	There is no mention of a submission. The purpose of having an approved protocol is to reduce the regulatory filing requirement by (possibly) one category. If, for example, a PAS change can now be filed as a CBE-30 under a comparability protocol, then the product cannot (should not) be distributed until after the 30 days. Therefore, the concern is that the paragraph makes no mention of filing. Since this section is intended to only address the submission of a CP and, given the last paragraph, when the CP is approved, how the results obtained for the product produced by the changed process should be evaluated, there is no need for this paragraph to address submission. The preceding is true because the next two sections ("IV. B." and "I V. C.") address how the outcomes of the evaluation procedure should be handled. This reviewer can only hope that the commenters, on reading this reviewer's remarks will see that their concerns are better addressed by the changes proposed by the reviewer. --- After the suggested changes were made, the referenced paragraph would read: "In all cases, a comparability protocol would be reviewed and approved by FDA prior to an applicant implementing a change under the protocol. 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. The following sections ("**IV. B.**" and "**IV. C.**") address what a sponsor should then do with regard to submitting the results of the sponsor's assessment and proceeding beyond the assessment."

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.B.	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 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~~.~~ 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.	Not all investigations and deviations may be pertinent to the change being made. For example, the presence of extraneous contamination must be examined, but is a cGMP compliance issue, not a registration issue. 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**.
IV.C.	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 this occurs, you can elect not to implement the change. 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.	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 <u>cannot</u> 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."

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.C. (Cont.)	276-282 (Continued)	Comment/Observation (Continued) Add to the end: Where unexpected data are gathered, the change should be evaluated to confirm that the product is not compromised and that the results are inconsequential. As stated, the sentence seems to be devoid of any 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' sentence contains little of value and 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. Essentially, it would "permit" the Agency to ignore non-compliance and treat the submissions as if the results found were compliant. 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 opposes the addition of the commenters' last remark. Thus, *whenever the submission requirements are not met,* the sponsor should choose either a) to not make the change or b) to generate and submit a PAS in support of revised specifications as the Draft states.	Rationale/Justification (Continued) 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, the change should not automatically be bumped 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 to 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. 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 need make no such provision as the Agency already has more than adequate mechanisms by which the sponsor may "discuss" issues with the **FDA** review groups. As previously stated, missing any **FDA**-approved acceptance criterion is of consequence as it clearly indicates that the sponsor does not adequately know its process. Thus, for good and sufficient reasons stated, the Agency should keep the draft text as it is here and incorporate that text in the final guidance.

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.D.	284-296	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 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 about 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 "obsolete."	General comment. Before commenting, the text cited needs to be reviewed **Lines 286** through **296** states, "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 comparability protocol are still appropriate prior to implementing and submitting a change under the protocol. 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." This reviewer would suggest the text be changed to: "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	Guidance Line	Comment / Observation	Rationale / Justification
IV.D.	284-296	Although the Agency intent is clear—to maintain use of appropriate protocols—the wording is ambiguous. Line 219—Replace "current FDA policy" with "current FDA Guidances". This reviewer does not agree and finds the commenters' rationale unsupportable. Line 295—specify how a protocol is withdrawn. This reviewer agrees, supports the commenters' recommendation, and recommends that withdrawals of submitted or approved CPs be reported in the firms' Annual Review. To accomplish this, the reviewer would recommend adding a short part (Part "**IV.F.**"): "**F. Withdrawal Of A Submitted Or Approved Comparability Protocol.** A sponsor may withdraw a submitted or approved comparability by submitting a "withdrawal" letter to the appropriate review division and, where appropriate, should report the accomplishment of that withdrawal in their Annual Review."	"Policy" is an overly broad term not restricted to CMC issues. "Policy" is the correct term because guidances are but a subset of Agency "policy." Thus, for example, if the Agency were to issue a policy that proscribed the use of stearic acid from animals sources and the sponsor's previously approved CP included the change from stearic acid from vegetable sources to stearic acid from animal sources, then, whether the CP is simply pending or has been approved, the sponsor should withdraw or modify that CP or, if pending, modify, that CP. Draft states that a protocol may be modified by a PAS submission (Part IV.E), but does not state how a protocol is withdrawn. PhRMA recommends the use of the Annual Report to withdraw protocols. This reviewer agrees that there is a need for a mechanism and would suggest that the mechanism be similar to that used for an application and, where the product is subject to annual reporting requirements, appropriately include the withdrawal of the CP in the firm's formal "Annual Review." The mechanism for withdrawals need to include the cases where the CP was submitted but not approved and where, though the CP has been approved, the underlying application has not been approved or, for the DMF case, the underlying DMF has not been accepted.
IV.D.	286-288	Screening for new infectious agents from a biological source is a dynamic state. Changes occur constantly as new technology and methods are acquired. Currently, there are no current compendial test methods available to quantitatively assess BSE/TSE risks. Would the CMC information required to obtain EU Certificate be satisfactory for FDA, or would FDA require additional/different CMC information for BSE/TSE safety assessments?	The commenters provided no rationale.
IV.E.	298-312	The wording is awkward. Is the FDA trying to state that when a parameter in an approved protocol is changed we can get the change approved and the protocol approved in the same submission, thus not having to get approval for both the parameter change and the protocol change separately? The use of a decision tree or flow chart would simplify the presentation. This reviewer agrees.	Clarity

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.E.	299-300	To avoid revising a protocol, it is recommended that, when predictable or possible, different options be submitted in the protocol. This reviewer disagrees. IF different outcomes are predicted for a change, THEN the process is obviously not adequately understood and/or controlled. When Predictable In such cases, the sponsor should not be using a CP but rather conducting whatever studies are needed to understand and control the subject processes. When Possible Even though it is always possible to submit different options, changes should be specific and have a single definite predicted outcome before the use of a CP is appropriate. This guidance clearly establishes the need for the outcome of a change to be predictable. Thus, the CP process should not consider the commenters' remarks as viable for a CP.	Need for flexibility. Need for protocol specificity, regulatory certainty, and **CGMP** compliance. If the changes proposed are predicted to have more than one outcome, perhaps a prior-approval submission or a supplemental application approach could be used. However, such are not amenable to and should not be the subject of a CP.
IV.E.	299-303	Changes to the protocol that provide increased control should be treated in the same manner as any CMC change that provides increased control. These should be filed as a CBE-30, not a PAS. This reviewer cannot agree. In such cases, the commenters should pursue the CMC change option they alluded to in their remarks.	Consistency and burden reduction. Since the use of a CP is optional, the commenters can, and, in such cases probably should, a) not use the CP approach and b) pursue the change by other suitable Agency-recognized approaches (such as the CMC change process alluded to by the commenters in their remarks).
IV.E.	303	Revisions to the comparability protocol should be tracked in the annual report, similar to the CMC index. This would be a sub-CMC index for changes made to the protocol over the life of the protocol.	Need a system to track the status of comparability protocols (modifications/deletions)

Section	Guidance Line	Comment / Observation	Rationale / Justification
IV.E.	316-317	It is stated that the notification of editorial changes to a comparability protocol can be provided in the AR. It is not clear what type of changes can be made/characterized as editorial and thus can be provided in the AR. A clarification is requested. Examples might be included. This reviewer agrees. To clarify what was intended, this reviewer recommends replacing the word "editorial" with the phrase "typographical, spelling, and grammatical."	Clarification of procedure to be followed and submission category to be used for modifications to an approved compatibility protocol. Since a CP is a technical document, it is not expected to and should not contain much in the way of "editorial" content. Given the preceding reality, it would seem that the Draft's intent here is to provide a defined mechanism for correcting typographical (e.g., "The ... 'process', ...," when the proper format is "The ... 'process,' ..."), spelling (e.g., "□omogeneity" when "homogeneity" is the correct spelling) and grammatical (e.g., "data are" when "data is" is grammatically correct) errors discovered after the firm's CP is submitted to the Agency.
V.	323	Change to include the underline text: "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.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.	325-328	Allow writing CPs as technology specific, across several products, or to address a change that affects the manufacturing of several or numerous products, particularly when the change is necessitated by new FDA or ICH guidances. For the reasons stated in the reviewer's previous "Observation" and "Justification" remarks on this issue, this reviewer cannot support this repeated attempt by the commenters to subvert the clear and proper use of a CP. While a "change" may affect several or numerous products and may be precipitated by a change in **FDA** or ICH guidance, the level of "change" required may not be the same for all and the "change" proposed may not result in acceptable outcomes for all. Therefore, this reviewer would again recommend that the Agency ignore the commenters' unsubstantiated and unsubstantial remarks. Allow for cross-reference of protocols between products. Indicate a mechanism for this to happen. There is no need to allow for this cross-reference between protocols as the sponsors are free to submit or reference submitted data packages in any other of their submissions. Thus, if a firm were to submit two CPs that were interrelated, they could reference each other's data to show general support for the change even though the "is comparable" data would be that supporting the "change" proposed in each separate CP. Moreover, this request has nothing that this reviewer can see to do with the cited text. Based on the preceding, this reviewer would recommend discounting the commenters' last remark in this case.	Writing a CP technology specific, across several products, 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 since all are in the one CP and require a PAS be initiated. How would this save time? It would be advantageous to obtain FDA agreement on how to file changes that could impact many products. For example, the improvement or development of a new method for evaluation of residual solvents used in the production of APIs. If the commenters' goal is simply to obtain agreement on a single change (as the example states) impacting multiple products, all they need do is file a set of CPs, one for each product, as a group. Often the same methods and same types of test data will be generated for multiple APIs each of which may be used in multiple products. As the comparability protocol is currently conceived such a change could require a separate protocol to be filed as a PAS for each drug product. This reviewer disagrees with what the commenters' supposition. Since the change in is the APIs, the firm manufacturing the APIs would only need to file a CP for each API that the change impacted. As long as each "post change" API is truly "comparable" to the "pre change" API, the drug product manufacturers would not need to and are not required to file CPs for their drug product process unless the change in the API process generated product that, though producing comparable drug substance batches, the drug substance is somehow not amenable to the drug-product manufacturing process and, thus, requires them to change sources or their drug-product manufacturing process.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.	330-334	Proposed change and the data to support it in a protocol should be in the context of current registration commitments. This reviewer disagrees, all proposed changes and the data to support them in a protocol must be considered in the context of **CGMP** compliance and not, as these commenters' remark states, "in the context of registration commitments." Example cited is not a good one. Beginning at **Line 328**, the example text being deprecated states: "**For example, a change in a fermentation medium component used to produce an antibiotic can result in more rapid cell growth, which, in turn, causes a higher production rate of antibiotic. Changes related to this change in culture medium could include modification in the length of cell fermentation, increase in harvesting time, and/or changes to purification columns. We recommend that you submit separate comparability protocols for unrelated changes.**" Based on what is said and this reviewer's knowledge and experience in this area, the example is an excellent one and should be kept.	The example cited implies that submitting a protocol for a simple raw materials change in a fermentation process would result (in the FDA's mind) in the need to assess aran ge of fermentation and product isolation parameters that are not likely to be registered or for that matter well enough understood to discern equivalence or differences before/after the change. This reviewer finds the commenters' rationale remarks very revealing. From the reviewer's experience, there is no such thing as a "simple raw materials change in a fermentation process." Furthermore, this reviewer agrees with the commenters' remark concerning " the need to assess a range of fermentation and product isolation procedures that are not likely to be registered" – there is a need and some firms have <u>not</u> reported the ranges and procedures needed to assess comparability. However, this reviewer finds the other part of that remark, "that are not likely to be ... well enough understood to discern equivalence or differences before/after the change," to be at odds with reality. Remembering a certain firm's change in a raw material that resulted in a new impurity that the firm even attempted to conceal from those in the industry that purchased the resulting API, this reviewer can see why the Agency chose this example and why it is on point and sends the appropriate message to the industry.
V.A.2, 3. & 4.	Entire Section (334-435)	Use of a decision tree or flow chart would simplify the presentation, in particular for validation requirements of release and/or development characterization testing. This reviewer agrees that the inclusion of a flow diagram and/or decision tree foreach subsection might assist the reader in determining exactly what is required. However, this reviewer disagrees with part of the commenter's rationale for the adding said decision tree or flow diagram (the term "flow chart" is usually more appropriate to an outline of a computer programming proposal).	Several concepts are presented in "dense" text. This reviewer agrees with the commenters. The appropriate extent of validation information to be provided in the CMC supplement (in particular for characterization testing reduced in a comparability protocol) is unclear and may be excessive. This reviewer disagrees with the commenters' assessment concerning the "extent of validation information to be provided." It is clear what is being requested just as it is clear what **CGMP** requires in this regard. <u>Unless</u> the commenters' definition of "excessive" is simply "more than they want to provide," the request to provide only some of what the **CGMP** regulations require the firm to have gathered and maintained is certainly not excessive.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.A.2.	368	Inclusion of stability protocol information into the comparability protocol. Since the preceding is the first of the two options provided in the guidance, this reviewer agrees with what is stated.	Cross-reference to an approved stability protocol should be adequate [**Comment:** It is not clear to me what we are recommending here] Since this is one of the options in the guidance, this reviewer agrees with the commenters' remark here.
V.A.2.	373	Add the following after 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 of the 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.	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 <u>not</u> agree with the commenters' proposed changes. However, 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 **CGMP** view is that validation is a journey and not a destination.	Generally, only limited analytical procedure information is provided to 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 that 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 info must be acquired and 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	Guidance Line	Comment / Observation	Rationale / Justification
V.A.3.	398-401	Change to include the underlined text: "The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided (e.g., in AR or CBE) when a postapproval 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 ~~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)."
V.A.5.	~~440-444~~	Revise this paragraph to read as follows: "The comparability protocol should identify the following information, which will be submitted to FDA at the time a post approval CMC change is implemented under the FDA-approved comparability protocol: 1. the type (e.g., release, long-term or accelerated stability data) of data 2. the amount of data (e.g., 3-months accelerated stability data). 3. the data that will be generated prior to distribution of the changed product, where appropriate (e.g., when the proposed category is a CBE-30, CBE-0, or AR)." In general, this reviewer agrees with the commenters' proposed changes but would suggest the improvements presented in the adjacent column.	The sentence is too long, leading to confusion. The sentence being discussed states, "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). This reviewer aggress with the commenters but would suggest: "The comparability protocol should identify the ~~following~~ information~~, which~~ that will be submitted to the FDA at the time apos t 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) ~~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)."

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.A.6.	455	The first sentence states that "...use of an approved comparability protocol may justify a reduction in the reporting category." Although the FDA intent that a protocol does not automatically result in a reduced reporting category is understood, this reduced regulatory burden is a primary motivator to the effort of submitting a comparability protocol for approval. [**Comment:** Is there a suggested revision here? If not, this should be deleted.] This reviewer agrees with the embedded "**Comment:**"	Most sponsors would probably not go to the trouble of preparing a comparability protocol if they would not get a reduction in reporting category. This reviewer fails to see the point of this comment and rationale – it simply states a general reality.
V.A.6.	460	FDA should clarify what the mechanism would be for reaching "agreement" with the applicant This reviewer agrees and suggests the following: A. The sponsor submit a written draft outline, B. An appropriate reviewing group then evaluates the outlinea gainst **CGMP**, the changes proposed, and the sponsor's compliance history, C. Based on the Agency's assessment, the Agency should: 1. Decline to suggest a reporting category, 2. Suggest the standard reporting category or 3. Suggest one category below the normal filing category for the changes proposed, and D. Send the sponsor their recommendations and the rationale used to reach the recommended category. E. The sponsor could then either: 1. Send a letter accepting the Agency's recommendation or, 2. Submit more detailed information that, in the firm's opinion, supports a different reporting category. F. When the sponsor objects, the Agency's formal dispute resolution process should kick in. G. At the end of the day, the Agency would then send the sponsor a letter stating that the assigned category with the caveat that "failure of the process or the product to meet any of its acceptance criteria nullifies any category reduction and will require a PAS to address the actual outcomes observed."	The commenters did not provide a rationale. All formal procedures need formal mechanisms to govern them. All formal mechanisms should be straightforward and self-documenting. At the end of the day, the final decision must ensure **CGMP** compliance and should be made by the **FDA**. This reviewer believes that the mechanism he has proposed can meet all of the preceding and is appropriate for the purpose stated. Moreover, this reviewer suggests that this procedure be contained in an appendix and referenced in the text of the guidance as and where the Agency sees fit.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.A.7.	463-469	Delete this paragraph. This reviewer disagrees with the commenters. The fundamental premise for a CP is that the sponsor has amassed sufficient data and, *based on that data*, understands the process to the point that it can prospectively project what the effects on the process or the product that each change will probably have. Thus, this reviewer finds the commenters' first "Rationale" statement disingenuous. If a sponsor can't project a course of action because the sponsor does <u>not</u> understand the probable process outcomes, then they should <u>not</u> submit a CP. With the replacement of the word "equivalent" with "comparable" previously proposed by this reviewer and minor changes designed to improve readability, the paragraph should be retained and state: **"It is anticipated that some changes in the manufacturing process will result in a postchange product that:** 1. **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~~** 2. **Does not meet the prespecified acceptance criteria in the protocol.** **You should identify in the protocol the steps you will take in such circumstances."**	As it is difficult to determine prospectively (without the actual data in-hand) what steps would be taken if equivalence is not demonstrated, this paragraph should be omitted. Apparently, the commenters think that a CP should be submitted even when the sponsor has no idea of the effects that a change may have on the process or the product produced by that process. Their thinking completely ignores the reality that a CP is an optional procedure that a sponsor should only use when the sponsor has a good understanding of the process and the effect of factor changes on that process. In such cases, the sponsor should be able to project the actions they plan to take if, in spite of their understanding, the results are not as expected. As the commenters state in the other remark, the sponsor may elect the PAS option. However, what a firm plans to do is left up to them. The Agency just expects them to understand their process well enough to project what actions they will take if a given acceptance criterion is not met. Moreover, if equivalence isn't demonstrated, why refer to the protocol? Most sponsors would merely submit a "standard" PAS and request approval based on the included data (with justification). Apparently, the commenters have gotten the proverbial cart before the horse, the request is what the sponsor plans to do in the event of failure before making the change – not what the sponsor does after the problem has occurred. There is nothing to prevent the sponsor from electing to do as the commenters suggest after the fact. Further, if this reviewer were reviewing a CP for acceptance and approval, this is one area where this reviewer would use the sponsor's contingency plans to assess how well they do understand their process and the probable change effects as well as the firm's approach to **CGMP** compliance.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.B.2.	494	Revise to add the underlined text: "... or that they are appropriately reduced, removed, or inactivated by ..." This reviewer does not agree with this change in the context of the text. This reviewer also has little respect for those who seek to suggest seemingly innocuous changes by taking the words from the text they wish to change completely out of context. However, the text should not be left as it is but changed to be more patient safety oriented as follows: "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)~~. In the case of new impurities or increases in the level of any existing impurity, the appropriate acute and short-term toxicity studies should be conducted. Based on the results of those studies, long-term toxicity and, in some cases, clinical studies may be needed."	In some cases, a low level might be good enough. The presence of a new impurity that is not removed in the case of chemical impurities or, in the case of biological materials, inactivated by downstream steps renders the products outside of the CP envelope because the products cannot be considered equivalent. This is the reason that the text states, "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)." Remembering the L-Tryptophan incident, the Agency would be derelict in exercising its safety responsibility to permit a process to have new impurities or increased levels of an existing low-level impurity without requiring the manufacturer to provide safety data that demonstrates the new impurities or the increased level of a given known impurity do not increase the safety risk to the public. Moreover, to be equivalent, the changed process must produce product that is no less pure than the current proposed (e.g., pending application), approved (e.g., NDA or ANDA), licensed (e.g., Biological product regulated as a drug) or accepted (e.g., DMF) product. For the reasons stated, the text should be changed as this reviewer suggests and not as proposed by the commenters.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.B.1.	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) ~~of the product produced using the old and new processes~~ 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 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 BACPAC 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, the 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 postchange product's comparableness to the prechange 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

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.B.2	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 ~~and~~, catalysts, and solvents."	As per BACPAC I, demonstration of equivalence includes assessing residual levels of existing and any new solvents.
V.B.2.	-	Add as the 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 the 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.
V.B.2	497-498	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 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 commenters provided no rationale. 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.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.B.4	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. 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,w ritten 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.C.	522-548	Since the regulatory filing requirements for the analytical changes would still apply, and the science surrounding analytical validation requirements is well documented, it is doubtful that the use of comparability protocols for analytical changes would provide significant sponsor benefit.	Time required might exceed timing of submission without approved comparability protocol, with little increased risk.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.D.	550-557	SUPAC guidance should be cross-referenced.	The commenters provided no rationale.
V.E.	559-579	Add to the end of line 579: "If a Site Inspection is required and would typically be initiated by the submission of a prior approval supplement, the applicant is responsible for insuring that the site has a satisfactory cGMP inspection in the type of operation prior to implementation 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, aswit h 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 inspection 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 accepted, be rejected and, if accepted or approved, should have their acceptance revoked or approval suspended until that facility has a satisfactory **CGMP** 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 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 a packaging site change to be reported in an annual review 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 necessarily provide for the use of such a Comparability Protocol, which places 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**FD C Act** and the implementing **CGMP** regulations.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.E.	570-579	If a change in manufacturing site is proposed for an aseptically processes product, would the FDA sanction the site change if the specific facility or area had successfully met a cGMP inspection within two years of when the comparability report was submitted? If not, would the successful media fill (3 lots) be satisfactory evidence if the last inspection period exceeded two years at the time the comparability report was 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 and, in the approval, 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 be automatically suspended pending a facility inspection update.	Clarification needed. 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 **CGMP**-compliant inspection status.
V.F.	581-586	Add to the ends of lines II.B., (L 114) and V.F. (L 586): "Comparability Protocols are not needed 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." 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.	Prior to 11/99 PAC Guidance, application 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 21 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 a 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.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.F. (Cont.)	581-586 (Continued)	Comment/Observation (Continued) 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.	Rationale/Justification (Continued) The 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.
V.H.	595-606	Spell out DMF/VMF holder and NDA/ANDA /NADA/ANADA holder responsibilities to communicating with one another when a comparability protocol references a DMF/VMF that is not held by the NDA/ANDA /NADA/ANADA holder. This reviewer does not think that the **FDA** has any authority in this area and should not attempt to get involved in what is purely a contractual matter between the sponsor and, if different, the DMF/VMF holder, or, when the DMF holder is located outside of the US territorial boundaries, the DMF/VMF holder's agent.	This section needs clarification. This reviewer disagrees because the clarification sought is outside of both the regulatory process and the **FDA**'s authority. To conduct a review that requires reviewing information in a DMF/VMF, the sponsor must obtain a letter from the DMF/VMF holder that authorizes the Agency reviewer to review the specific part of the DMF that bears on the sponsor's submission. How the sponsor deals with the DMF/VMF holder to obtain the requisite DMF/VMF "review" letter, is strictly up to the sponsor. The preceding is the case because DMFs/VMFs are trade secret filings.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.H.	599-606	Change from: 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. Change to: The DMF holder should confirm that changes are properly reported to the FDA. Additional updates may be 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 all other DMF/VMF submissions. *Unlike the drug product AR*, it is not automatically reviewed nor is it automatically reviewable.	The Guideline for Drug Master Files (September 1987) 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 file or, perhaps a different portion of a master file. However, 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 the existing sections of a master file. A new letter is needed because in support of the CP, the DMF/VMF holder will have added new information to the DMF/VMF 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/VMF 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/VMF 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/VMF holder provides a letter authorizing the Agency to do so. [**Note:** In light of this reality, perhaps the industry should be lobbying for annual inspections for all DMF/VMF 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 ensure that components that are different than the components listed for the firm's approved or licensed drug product are not used to make drug product. The DMF/VMF holder's responsibility in such cases is clearly secondary.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.H. (Cont.)	599-606 (Continued)		Rationale/Justification (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 authorization letter is unnecessary since the FDA must have received the DMF letter at the time of the 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. Therefore, each time a DMF-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. As DMFs are not "approved" documents, how is the Comparability Protocol to be approved when submitted to a DMF? How is notification of "acceptance" of the Comparability Protocol received? 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 by a DMF/VMF holder and not review it until a) the holder's next inspection or b) it is referenced in a drug product filing. If the NDA/ANDA/NADA/ANADA holder submitted a CP protocol referencing the same DMF/VMF process and product, it would be either approved or rejected. In **Case 1**, review during inspection, only the DMF/VMF holder would be notified; in **Case 2**, both holders would be notified (DMF/VMF holder in its EIR letter, and the others by an approval letter). In latter case, a DMF/VMF holder letter would be needed authorizing the Agency to a) review the appropriate DMF/VMF files for the CP and b), when the CP studies have been completed, again review the up-to-date files as a part of the Agency CP-report review prior to authorizing shipping the post-change product

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.I.	608-617	This section implies that a DMF/VMF can be changed using a comparability protocol. This section does more than imply, it states that a DMF/VMF can be changed using a comparability protocol that the Agency would not ordinarily review. Thus, determining the validity of CPs submitted by DMF/VMF holders falls on the inspectorate and those firms that use the product produced under the DMF/VMF. We would like to see this clarified. Changing a DMF/VMF under a comparability protocol is another of those changes potentially impacting multiple products manufactured by multiple drug product manufacturers. This reviewer agrees with the commenters' remark. Would the DMF/VMF (e.g. API) and corresponding NDA/ANDA/NADA/ANDA (e.g. Drug Product) protocols need to cross reference one another? The DMF/VMF has no need to cross reference any of the firms that purchase the DMF controlled products (**see "Discussion 1"** in adjacent column). Sometimes the drug product manufacturers are unwilling to divulge the use of an API produced under certain DMF/VMFs. Failure to disclose the true source of an API to the Agency "adulterates" the drug product produced and makes the offering of said drug product for sale a violative act that subjects those who release such drug products to criminal penalties. Hopefully, the commenters will work with the Agency to identify and excise such persons from the drug product industry.	Clarify the section. **Discussion 1** Further, because DMFs/VMFs are "trade secret" documents, except for cause, the Agency does not ordinarily have any authority to review a CP so submitted unless a drug product manufacturer explicitly files a submission that addresses the CP and provides the Agency a review authorization letter from the DMF/VMF holder. The drug product manufacturers do have a compelling interest in seeing to it that the changes implemented produce comparable product. This is the case because a change that leads to a postchange product that is not comparable could put them out of business – they are not approved to use such APIs. Thus, to ensure that the components supplied by a DMF/VMF holder are the same as the components supplied in the submission documents, the drug product manufacturer needs: 1. Strong contractual incentives for the DMF/VMF holder to collaborate with them for proposed changes and 2. Specific identity test suites that are designed to detect undisclosed changes. 3. Rigorous specifications for all variable factors (chemical and physical) that can affect the safety, efficacy, and conformance to **CGMP** of the drug products made with each such component. In the reviewer's experience, most firms are willing to do whatever they can to satisfy their customer provided the customer is willing to pay for the added costs for doing it. For example, Dow was more than willing to provide a small drug product manufacturer of sustained-release drug products with a very special grade of "Methocel" at an additional cost of only $US 0.03 per kilogram even though, *on average*, only 4.5 lots/month of their production met Dow's special release criteria and only 2.5 lots/month of their production lots met the drug product firm's rigorous acceptance criteria.

Section	Guidance Line	Comment / Observation	Rationale / Justification
V.I.	610-617	Recommended verbiage: The provisions for submitting a comparability protocol to a master file 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 these 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 postchange 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 have 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 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 **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 ther isks they elect to take. If a 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 and make other sourcing arrangements.

Bristol-Myers Squibb Pharmaceutical Research Institute's Submission, Dated June 19, 2003, To Docket 03D-0061: "C-12"

[**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 commenter.]

These commenters begin by stating, "Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2002 alone, Bristol-Myers Squibb dedicated $2.2 billion for pharmaceutical research and development activities. The company has more than 5,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises of approximately 50 compounds under active development. For these reasons, we are very interested in and well qualified to comment on the FDA draft guidance for industry entitled 'Comparability Protocols – Chemistry, Manufacturing, and Controls Information'. Specific comments are provided in bullet format below."

- Reference is made to lines 288-301. Modifications to a comparability protocol should be reported and approved according to the appropriate reporting category for the change. For example, a change in a test method to comply with an official compendium would be filed in an Annual Report. If this change in test method also affects an approved comparability protocol and the protocol is referenced as part of the request to make the change, the modified protocol should be acceptable for use because the change is considered minor."

This reviewer does not agree with the commenters' proposal.

If nothing else, it is too simplistic.

For example, it does 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.

In case "a)," this reviewer would agree with the general reporting of the change (in the Annual Report) but would suggest that the sponsor submit the update to a protocol under review as an addendum.

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. [**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.]

- "Please provide further clarification on the expectations for a 'detailed description' as listed in line 327 – 'a detailed description of the proposed changes clearly.....'. Too much granularity in the detailed description will limit the usefulness of a given protocol since it will be difficult to anticipate the precise nature of every change that is to be made in the future as a result of development work. For example, a comparability protocol could be filed for modifications to a complex fermentation process without detailing what components or conditions would be changed."

This reviewer does not agree with the commenters' remarks.

If a firm does not understand their process and the factors that affect the quality of the product produced, then that firm: **a)** should not change their process, **b)** should not pursue the filing of a comparability protocol until they do understand their process, and **c)** should conduct studies that provide the data needed to understand their process.

In the absence of understanding, making a change is, at best, a gamble.

Moreover, it is hard for this reviewer to believe that a process that is not understood can be **CGMP** compliant.

For all of the preceding reasons, this reviewer recommends that the Agency reject processes where understanding of the process is not demonstrated such as the commenters' hypothetical example "fermentation process" and continue to require the changes to be detailed.

Finally, the only sentence that this reviewer could find that contains the commenters phrase, "a detailed description of the proposed changes clearly...," is in **Lines 340** and **341**, "A comparability protocol should provide a detailed description of the proposed changes clearly identifying all differences from the conditions approved in the application" and not in **Lines 326** through **328**, "Each change should be specified and the acceptance criteria for evaluating the effect of the changes should be well defined" (the underlined text is the text in **Line 327** in the ".pdf" version of the Draft).

This reviewer's bottom line is that firms that cannot do what the Draft requests should neither change the process steps thatt hey do not understand nor submit a comparability protocol for such process steps.

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

GlaxoSmithKline's Submission, Dated July 1, 2003, To Docket 03D-0061: "C-11"

[**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 commenter.]

These commenters begin by stating, "Enclosed please find comments from GlaxoSmithKline, both general and specific for the Draft Guidance for Industry on Comparability Protocols – Chemistry, Manufacturing, and Controls Information. These comments are presented for consideration by the FDA. The specific comments are presented in order by the section of the guidance. GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this guidance."

"General Comments:

The document contains ambiguities that need to be defined or explained. The guidance should define comparability protocol, bioequivalence, equivalence, and equivalent product."

This reviewer disagrees with the need for the definition of equivalence and equivalent product.

This is the case because the correct terms are "comparable" and "comparable product."

The as the Draft's title phrase, "Comparability Protocols," clearly indicates the goal is to determine comparability not equivalence.

Therefore, this reviewer would again request that the Agency replace all instances of "equivalence" with "comparability" and "equivalent" with "comparable." (**See Review of C-14.**)

"Provide clarity on where statistical equivalence is required and where meeting the approved acceptance limits is acceptable to demonstrate equivalence."

This reviewer finds that statistical quality control is a requirement for the drug product (**21 CFR 211.165(d)**).

Therefore, under **CGMP**, *comparability* must be defined by the appropriate statistical treatment of the data for drug products.

In simple terms, *statistical quality control* assessments on the results from the appropriate *batch-representative samples* from *each batch* must predict that *each batch*, not just the samples that the firm happened to have tested, will, if tested, meet the acceptance criteria established in the comparability protocol.

Since the Agency's position is that, where applicable, the drug product **CGMP** regulations are to be used for the drug substance, the post-change comparability of the drug substance should also be *statistical comparability* oft he batch not just that the samples tested happened to meet the acceptance criteria established.

"There are no references to other bioavailability/bioequivalence guidance documents or profile or non-profile methodology using population bioequivalence methodology."

"Specific Comments

Section II.A. What is a Comparability Protocol?

Inclusion of FDA's responsibilities for providing input on a comparability protocol proposal should be included in this section."

This reviewer does not agree.

Since this document is guidance for the industry, it would not be appropriate here.

These issues should be a topic to be considered in the guidance it provides to its staff.

"The FDA should give guidance within a defined amount of time so that the sponsor can know if the protocol is acceptable or not, before commencing work."

If possible, the Agency should consider setting an "Initial Review" window (for comparability protocols that are reviewable [those from other than DMF and VMF holders]) after which a "Preliminary Assessment" form would be sent to the submitting firm.

The sponsor could then use that firm's assessment of the form to decide how best to proceed.

However, there is nothing that prevents a firm from using small-scale "comparative" experiments to verify that the change produces comparable product, establish scientifically sound and appropriate acceptance criteria, write the comparability protocol, and then submit the protocol with the assurance that the post-change process produces product that is comparable to the product produced by the pre-change process.

"Section II.B. When Might a Comparability Protocol Be Useful in Making a CMC Change?

The Agency should consider that multiple changes can be described in a matrix and that the changes do not have to be "related". Multiple, unrelated changes should be allowed if the analysis is appropriately designed."

This reviewer has no problems with the use of a matrix approach to describing changes to a single process so long as the descriptions are specific and the appropriate testing is to be performed and scientifically sound acceptance criteria have been established for each.

Since the Draft does not absolutely rule out incorporating changes in a single process that are not "related" into the same comparability protocol, this reviewer can only caution the commenters that it will be much more difficult for the firm to address comparability protocol failures when the comparability protocol includes several unrelated changes.

Finally, in this reviewer's limited experience, firms that seek to make multiple "unrelated" changes often do not adequately understand their processes.

However, the Agency should, in general, reject comparability protocols that seek to make multiple "unrelated" changes in multiple products or even multiple "related" changes in multiple products because of **a)** the ambiguities in review and review timeframes that such situations cause and **b)** the reality that a failure in any one product fails the entire set of products in the protocol.

To assist the Agency, the guidance could explicitly state that, once submitted, the Agency will either approve or reject the protocol as a whole regardless of the nature of the deficiency or the number of products impacted.

In this manner, the Agency will make it clear that "bundling" is discouraged and will lead to the Agency's rejecting the protocol for all of the products in the protocol when any one change is deemed to probably generate a non-comparable product.

Further, should a multiple product protocol be approved and any one product found to be non-comparable in the post-approval studies, the Agency will reject all of the products in the comparability protocol.

This is the case because the Agency approved the protocol contingent upon its producing comparable product in all cases.

Thus, a failure in one product in a multiple-product comparability protocol would, *at a minimum*, trigger the PAS reporting requirement for all products in such protocols because their reporting status is tied to the protocol and not to the individual products in a multiple-product comparability protocol.

"Section IV.A. How Should a Comparability Protocol Be Submitted?

The Agency should define the length of time it will take them to respond to the sponsor's request for review and approval."

This reviewer disagrees.

Since the Agency has classified comparability protocols as PAS documents, the times are those clear PAS timeframes that the Agency has defined.

Moreover, the reality is that the better a firm establishes: **a)** that it knows and understands their process and **b)** the higher the level of certainty that supporting data establishes, the more likely their comparability protocol is to obtain approval and the overall review time to be minimized. [**Note:** However, unless triggered by a supplement from the drug product manufacturer and supported by an appropriate authorizing letter, comparability protocols submitted by DMF and VMF holders will not be reviewed and, absent the preceding, should along with the post-change comparability report generated be reported in the holder's annual submission.]

"Section IV.C. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?

The Agency should define possibilities for a discussion with the sponsor to resolve issues with data that would prevent having to submit a prior approval submission."

This reviewer disagrees.

If the product fails to be comparable, there is nothing to discuss.

This is the case because a true "comparability" failure clearly indicates that the submitting firm does not truly understand its process and the post-change product is neither approvable or licensable, nor acceptable.

In such cases, the firm needs to continue making the approved, licensed or accepted product until they find a change or changes that do make comparable post-change product.

In the science-based regulatory environment required for risk-based decision making, valid risk-based decisions can only be made when the science-based population data is available to predict the risk.

Since there is no such database (toxicological and clinical) for the population risk for non-comparable product, the Agency can only accept the change when the product is comparable and reject it when it is not – risk-based decision making is not supposed to be based on speculation.

If the Agency needs a clear example, let them remember that **FDA** administrator who decided to "authorize" the release of a particular batch of polio vaccine because it almost met the stage one limit for wild virus – that decision injured 100's of those who received that lot and put some in iron lungs for the rest of their shortened lives.

"Section IV.D. When Does a Comparability Protocol Become Obsolete?

Clarity is needed on what is obsolete and what is not. If a process works and is validated, but does not use new technology (software or equipment), is it obsolete? Who makes the decision about when it is or becomes obsolete? What is the determination of comparability protocol that is obsolete?"

While this reviewer recognizes the commenters' concern, the context **only** applies to the compatibility protocol and not to the process, the technology, or the equipment.

To clarify this, this reviewer again recommends that the text in **Lines 286** through **296** be changed 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, through review or inspection, 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 IV.E. How is an Approved Comparability Protocol Modified?

Clarity is needed for using a comparability protocol when it allows for a revision that is minor; can the revised comparability protocol be reported as a CBE-30 rather than a prior approval submission?"

This reviewer does not agree.

Only when the revision is triggered by an outside agency like the ***USP***'s changing a protocol analytical test method that is **tied** to the ***USP*** method before the approved protocol can be executed should the Agency consider reducing the filing category for an approvable comparability protocol from PAS to a lesser status.

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.

"Section V.A.8. Commitment

Define obsolete."

Though this reviewer sees no need to define the term "obsolete" beyond the dictionary's "out of date," this reviewer recommends the following definition

> **"Obsolete**: 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.E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?

Clarity is needed about the need for a comparability protocol when using or changing contract analytical facilities."

As a Ph.D. Analytical Chemist and sometimes auditor of contract laboratories, this reviewer is all too aware of a need for some mechanism for the firm to verify that the results obtained by one lab are valid and truly comparable to the results obtained previously.

However, because a comparability protocol (CP) is an optional approach to satisfy the Agency's need to know that a firm's manufacturing systems, processes and products are in compliance with **CGMP**, the use of CP to accomplish this is up to each firm.

Whatever a firm elects to do in this regard, the Agency's overriding goal is to ensure that the post-change product batch is comparable to the pre-change product batch.

Changing testing laboratories can impact batch comparability especially given the batch acceptance requirements set forth in **21 CFR 211.165(d)** that require that not only must the test results found meet specification but also that statistical quality control (SQC) must predict that the batch is acceptable before it can be released.

If the overall result uncertainty in the proposed laboratory is more than that found in the current laboratory, the SQC acceptability of the batches will not be comparable and, for the same acceptance criteria, more batches will fail to meet the criteria.

Conversely, if the overall result uncertainty in the proposed laboratory is less than that of the current laboratory, the laboratories are, by definition, comparable

and, even though the risk of a predicted batch failure decreases, the firm and the Agency should welcome this change.

"Section V.F. Can a Comparability Protocol Be Used for Container Closure System Changes?

Examples of acceptable comparability protocols for different dosage forms (including inhalation and nasal products) would be helpful."

"Section V.I. Can a Comparability Protocol Be Included in a DMF or VMF?

This section states that comparability protocols are product specific yet a DMF is not always product specific. Clarity is needed to understand how a comparability protocol could change a DMF."

American Dental Association's Submission, Dated July 1, 2003, To Docket 03D-0061: "C-10"

[**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 commenter.]

As of 18 October 2003, the comments made by these commenters have not been made available to this reviewer.

Johnson & Johnson Pharmaceutical Research & Development, LLC's Submission, Dated June 25, 2003, To Docket 03D-0061: "C-09"

[**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 commenter.]

These commenters begin by stating, "The above referenced FDA draft guidance entitled Comparability Protocols – Chemistry, Manufacturing, and Controls, issued February 2003 has been reviewed by scientists at Johnson & Johnson Pharmaceutical Research, LLC. The following comments are provided for your consideration."

"General Comments
This draft guidance attempts to be responsive to industry's need for more predictable, resource-efficient, and scientifically sound regulatory pathways for post approval changes made to pharmaceutical drug substances and products. Our scientists appreciate the potential benefits of defined protocols but have the following major concerns:
In order to enhance the usefulness and effectiveness of comparability protocols to industry, a higher level of protocol review is requested at FDA. We recommend that a Comparability Review Committee (similar to the SUPAC Review Committee) be established to oversee protocol practice in order to ensure consistency across divisions on various issues, to shorten approval times and to provide further guidance such as Question and Answer documents for the benefit of industry."

This reviewer does not agree.

If better consistency is sought, then the Agency should be requested to issue a corresponding guidance to its review and inspection personnel.

Given the level of competence demonstrated by many of the supposedly science- and/or regulatory- based committees within the Agency, adding another such committee would increase the already excessive bureaucratic overhead in the Agency and contribute to the ever lessening role that sound science plays in Agency decisions.

"The requirement for early submission of highly defined protocols seems to suggest that all process changes, container-closure component changes, analytical detection requirements, etc. are anticipated at NDA filing or early in the review process. In fact many changes are not anticipated and detailed information impossible to provide."

If a firm does not truly understand their process, that firm should simply not use this already optional approach to demonstrating **CGMP** compliance and use another route.

"If provided, the level of specificity may define the protocol so narrowly as to diminish future usefulness. If specifics are provided, protocol amendments would likely be required later as additional information and experience is gained. This would diminish the usefulness/benefits of using protocols. Further clarification and guidance is requested from FDA to achieve a workable balance between the need for specifics and the realistic limits of industry information and experience."

This reviewer disagrees with the commenters' remarks.

Firms that do not truly understand their processes and the products produced by these processes should not use the "comparability protocol" approach to regulatory compliance until these firms fully understand:

1. **CGMP** (and comply thereto),
2. What constitutes sound science (and use sound inspection science in their studies and specification setting), and
3. Their processes and products.

The reality is that the limits of industry ignorance are almost always self imposed.

Most firms seemingly do not want to know because if they know then they will have no excuse for their non-compliance.

"Several more general comments are offered for your consideration, followed by a listing of major and minor comments by section and line number.

- As noted in Section III B, reporting changes under an approved protocol would normally result in the reduction of a reporting category. This outcome is clearly beneficial and examples of the types of changes where this reduction may apply would be extremely valuable."

- "The draft guidance states in Section III A, that protocols may be used effectively for changes to the container-closure system and other changes of a repetitive nature.
  When multiple related and repetitive changes are involved, particularly with container/closure system changes, may the requirements of the protocol focus on the "worst-case" changes such as a new closure on the smallest container, etc?"

  "Would it be permissible to 'Bundle' protocols to facilitate multiple related changes across products lines?"

  In general, this reviewer and the Draft do not support this approach.

  "Specific reference to (and more detailed explanation of) the potential requirements for Sunset Testing, Skip Testing and other testing theories under the protocol system would be extremely valuable."

Under **CGMP**, "Skip Testing" is violative of the explicit representative sampling and testing from each shipment, lot, or batch depending upon the context and should not be discussed.

"Sunset testing" is a CMC issue that is not amenable to a comparability protocol because the comparison required (without testing to with testing) must be for tests that are outside of **CGMP**. [**Note:** A test that can be dropped is, of necessity, one that is in addition to those required by **CGMP** (incoming acceptance, in-process at the start or completion or across each phase/step/stage in the process, drug-product for release, drug substance and drug product for post release stability, and drug product post-release annual inspection and complaint handling).]

Comparability Protocols are for items covered by **CGMP** (processes, controls, and products).

As far as this reviewer is aware, comparability protocols are not amenable to "testing theories;" they require the firm to do **CGMP**-compliant inspection (sampling, and testing or examination) on batch-representative samples from each lot or batch for every aspect and stage of the process.

> "Specific guidance regarding the potential requirements for changes to BCS I category products would also be greatly appreciated.
>
> Our scientists have expressed a general concern regarding the benefit of submitting comparability protocols versus a potential increase in the number of submissions required to gain approval of a post approval change as described in the SUPAC guidance. The benefit of a reduced reporting category in some cases may be outweighed by the need to submit the comparability protocol in advance, keep it updated or alternatively withdraw it."

This reviewer agrees that it is up to each manufacturer to decide which path is the better one for their organization.

> "It would be useful to include further discussion of the benefits to industry balanced with the "costs" of submitting and maintaining protocols throughout the product lifecycle, addressing the following issues:
>
> - The mechanism for withdrawal of a Comparability Protocol"

This reviewer agrees that this is a topic that the Agency should include in the guidance.

- "Under Section IV.A., if a comparability protocol for an unforeseen change is not submitted in the NDA, an additional Prior Approval Supplement would be required. Please provide clarification regarding the advantages of submitting protocols via the Prior Approval Supplement route. While it is clear that submitting protocols at the time of filing may decrease the future regulatory filing burden, submitting protocols via Prior Approval Supplements (with or without supporting data) offers few filing advantages and is essentially similar to current filing practices."

Since a CP is a form of PAS, submitting it with a filing or in a PAS is effectively the same from the viewpoint of a timelines.

Moreover, all CPs are supposed to be submitted with supporting data.

All a CP is designed to do is speed the "PAS" review process by ensuring that the submitter provides the needed body of evidence that clearly establishes the CGMP compliance of and the probable comparability of the post- and pre- change product.

For those who truly understand their processes, a CP should be easy to justify when during development or after approval, license, or acceptance, the firm finds a better way to make the same product or a way to make the same product better and wants to implement that change.

If the commenters do not see the advantage to themselves or the Agency's submission reviewers of having a well-defined outline or road map to follow, then this reviewer would suggest that they continue using their current approaches.

- "The mechanism for discussing comparability protocols with the reviewer prior to a non-approval letter or other adverse ruling so that approvals are not negatively impacted"

This reviewer would suggest that the Agency provide a mechanism where the "discussions" are written, not verbal, and the communications are tracked and

proceed though a supervisory chemist to reduce the direct pressure on the reviewer to change his or her findings.

- "If protocols are used aggressively, there may be a 'perception' that product development is weak, thereby jeopardizing dossier approval"

This reviewer agrees and would add that, in his experience, perceptions of this sort are often not far from reality.

However, the preceding is just another one of those things that a firm must weigh against its haste to get the product to market.

If nothing else, this Draft and the comments made to it should greatly assist the review chemists in their efforts to determine if a submission: **a)** is **CGMP** compliant and **b)** ensures that the process, controls, and product are, with a high degree of certainty, **CGMP**.

- "Changes reportable under an Annual Report or Changes Being Effected Supplement will take longer to implement when reported under a protocol"

Other Comments by Section:

"Part II A

- Line #97: "*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.*
  This definition references the drug product and not the drug substance. Reference to the drug substance should be included."

This reviewer agrees and would again propose the following alternative text (**Lines 97** through **99**):

"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."

"Part II.B.

- Line #109: "Furthermore, because a detailed plan will be provided in the comparability protocol, the FDA is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception).
  The term 'less likely' is vague. The sentence should be revised to read '*...it is anticipated that the FDA would not need to request additional information to support changes made under the protocol.*'"

This reviewer disagrees with the commenters.

Though "less likely" may be vague, it properly conveys the Agency's perception of what may be the case.

What will be the case cannot be known at the present time, and, if ever, will not be knowable until after the final guidance is issued and the Agency gains experience with the CPs submitted.

The Agency's anticipation, based on their experience with other such guidances, is that it is "less likely" and that should be good enough at this time.

- "Line #112: '*The use of a comparability protocol could allow an applicant to implement CMC changes and place a product in distribution sooner than without the use of a comparability protocol.*'
  The word "could" should be replaced by "will". The sentence should be revised to read "*The use of an approved comparability protocol will allow an applicant to implement CMC changes and place a product in distribution sooner than without the use of a comparability protocol.*"

Again, this reviewer cannot agree with the commenters' presumptuous change. If an applicant submits a deficient CP, then what will be the case?

The use of "could" is appropriate because the Agency has no direct control over the sufficiency of the CPs submitted and again has no experience base to draw on to frame their remark any more positively here than the Agency has.

As with any tool suitable for a given task, it only facilitates the task when it is properly used.

"Part II.C

- Line #117: **For many years, applicants (upon FDA approval) have used protocols to implement certain types of CMC changes (expiration dating period extension, container-closure component interchangeability, etc.)**
  Would these protocols need to be updated or withdrawn to comply with the requirements set forth in this draft guidance or be grandfathered?"

As with any other similar guidance document, it mandates no course of action and its use is in the control of the firm that wishes to use it as a tool to aid its compliance activities.

Since the use of a CP is both optional and considered as an adjunct protocol, no other guidance is directly affected by this guidance.

Based on the preceding, this reviewer does not foresee any such problems because this guidance does not establish any requirements.

It simply provides a path that a firm may, or may not, choose to use, as all guidance documents do.

"Part III. C

- Line #211: "*A CMC change that requires efficacy, safety (clinical or nonclinical), or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities)*"
  The word "clinical" should be added. The sentence should be revised to read "*A CMC change that requires clinical efficacy, safety (clinical or nonclinical), or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities).*" The implication from this section is that a protocol should not be used for BABE studies. More specific information on the types of CMC changes that are inappropriate for protocol use would be very helpful."

This reviewer agrees.

Non-clinical efficacy (Dissolution and Drug Release) studies fall under the umbrella of what a CP seems to be designed to address.

- "Line #217: '*Specific examples of changes that may be difficult to justify under a comparability protocol can include (list of examples):*'
  Please provide specific information on the rationale for excluding these examples from protocol use."

"Part IV.D

- Line #283: "*When Does a Comparability Protocol Become Obsolete?* "
  Clarification is requested regarding how a protocol is determined to be obsolete. Does FDA anticipate making this determination or assigning an expiration date? A provision should be added to permit the "review of an existing protocol without submitting it as a prior approval supplement."

This reviewer suggests the commenters should reread the current text and the reviewer's proposed alternative.

In both cases, the text clearly states that the submitter has the onus of determining when an approved CP is "obsolete" (out of date).

From the Draft's text, it is clear that the **FDA** does not **"anticipate making this determination or assigning an expiration date."**

The commenters' last statement is inappropriate in the context of this section and should be ignored.

If a firm takes a risk and submits a CP before it understands its process, then that firm should be prepared to shoulder the cost of their precipitous action when they find that the process must be changed again or that the proposed change is untenable.

As was stated earlier, the only area where the Agency should consider adding flexibility would be for method changes that the holder of the approved CP is compelled to make to satisfy an outside non-governmental organization's requirements (like the ***USP***).

"Part V.A

- Section 2, Line #374: '*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.*'
  Please provide an example of when stability studies would not be needed."

Example: The proposed change is to increase the number of film coats on a film-coated immediate-release tablet to improve tablet appearance that, based on *lab-scale* studies, only slightly changes (< 0.3 % on average) the initial "Dissolution" of the tablets. In this case, the only comparative studies required would be "Dissolution" studies on the finished tablets.

- "Section 418: '*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 post-change material.*'
  Further clarification is requested for this paragraph (i.e. whether specification and process changes can be included in the same protocol)."

"**Part V.C**

Line #527: '*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).*' **The phrase '*...do not significantly change*'...should be changed to '...does not adversely change'. The sentence should read as follows "The comparability protocol would be designed to demonstrate that the proposed changes in the analytical procedures improve or do not adversely 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)."**

This reviewer agrees with the commenters' suggestion and notes that it is refreshing to see that a new test method is comparable to a previous test method ***if and only if*** it improves or does not adversely impact the test method's critical validity attributes.

This reviewer only hopes that a post-change product will likewise only be recognized as comparable to a pre-change product when the change improves or does not adversely impact the product's critical validity attributes (safety, efficacy, identity, strength or potency, quality, purity, and stability).

- "Line #545: '*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.*' **The following text should be added, 'Except where the new method provide better or equivalent QA and assures the safety, efficacy and quality of the product.' Therefore, it is recommended that the sentence should be revised to read '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, except where the new method provides better or equivalent QA and assures the safety, efficacy and quality of the product.'"**

This reviewer does not agree with the commenters' suggestion because it is at odds with reality.

The "**relaxation of acceptance criteria**": **a)** has nothing to do with the test method change *per se* and **b)** cannot "**provide better or equivalent QA.**"

However, the addition of a new test may be permissible in cases where the new test measures attributes in one test procedure that previously required two test procedures

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

Novartis Pharmaceutical Corporation's Submission, Dated June 24, 2003, To Docket 03D-0061: "C-08"

[**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 commenter.]

These commenters begin by stating, "Novartis Pharmaceuticals Corporation is a world leader in the research and development of products to protect and improve health and well-being. Novartis researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis. The company's mission is to improve people's lives by pioneering novel healthcare solutions. As a global pharmaceutical corporation, Novartis is supportive of efforts to improve and to harmonize the technical requirements for registration of pharmaceutical products. We appreciate the opportunity to comment on this guidance in accordance with FDA's Good Guidance practices. Novartis supports the concept of comparability protocols, based on the successful use of such protocols in past FDA interactions."

General Comments

"However, Novartis is concerned that the usefulness of comparability protocols might be dictated by how well they fit into project timelines, when compared to current Prior Approval Supplements done without benefit of comparability protocols."

Since, as proposed, a comparability protocol is an optional adjunct to a filing or a PAS, this reviewer does not share the commenters' concern.

Because it is an adjunct procedure that is optional, each firm can choose to use this approach to addressing Agency concerns, or not use it, as that firm sees fit.

Like the proposed "Development Report" in the companion draft guidance on CMC Information, it is but one means that a firm can use to provide the information needed by the firm and the Agency to ensure:

1. The firm's proposed changed process and/or controls are projected to be and will probably be **CGMP** compliant before the changes are initiated and
2. The firm's post-change product will:
   a. Be **CGMP** compliant and,
   b. With a high degree of assurance, probably be "comparable" to the pre-change product.

"Novartis is also concerned that the Guidance, when finalized, clearly indicate how complete FDA input into the protocols by all involved departments will be obtained."

While this reviewer shares the commenters' concern, this reviewerd oes not think that the guidance to industry is the place for such commentary.

Therefore, this reviewer suggests that the Agency issue a companion guidance t for Agency personnel or update a current such guidance as the Agency sees fit to

address the commenters' concerns about the internal workings of the review of a comparability protocol.

"These points are elaborated and additional comments are provided in the attached tabular format, for ease of FDA use."

Major comments

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
General Comment	The usefulness of comparability protocols will be dictated by how easily they fit into overall project timelines. Two points could be addressed: reduced FDA Approval timeline for comparability protocol review and comment (rather than 4-6 month current PAS requirement) While this reviewer agrees with the "reduced ...timeline" sentiment expressed by the commenter, the reviewer would cast their first point in terms of "*reduced **FDA** review timelines for comparability assessment and comment*" and leave it up to the Agency to set timelines based on protocol complexity and length rather than those based on arbitrary dates. Inclusion of other FDA groups (Tox/Biopharm) in protocol review to assure completeness of FDA response	In some cases, it will be faster to call the FDA with a specific question, documenting the teleconference, rather than waiting for the approval of a Comparability Protocol in a PAS, and then completing the work and submitting the application (with reduced submission reporting category) to FDA. Though the reviewer finds the commenters' remark not directly pertinent and interesting, this reviewer would strongly recommend that no **FDA** official engage in such practices – all questions bearing on any aspect of **CGMP** should be submitted in writing (e-mail or FAX) and an appropriately vetted response written response (e-mail, FAX or letter, as appropriate) issued. Since it is not appropriate for an **FDA** employee to give advice that does <u>not</u> conform to the requirements of **CGMP**, the Agency would be better served by a) written requests so that what is being requested is clear and b) written response since, unlike verbal discussion, it is a) much more difficult to distort by taking passages out of context and b) easier to track in existing database structures. Some points such as impurity qualification or dissolution evaluation include FDA groups in addition to the CMC reviewers. This reviewer agrees and notes that some changes in equipment, process control point, or inspection plans (sampling, and testing or examination) would benefit from the input from the Field Inspectorate, Manufacturing and Product Quality, and Statistics.
Lines 110-112	Would the FDA Review Chemist take on the role of distributing comparability protocols that cross FDA disciplines, and providing a consolidated FDA response to the NDA sponsor, or would the sponsor need to send copies for binding comment to other FDA groups?	CMC elements such as comparative dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Clarification of the administrative process needed to obtain a binding FDA agreement on the Comparability Protocol is requested.

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
Lines 284-296	Although the Agency intent is clear – to maintain use of appropriate protocols – the wording is ambiguous. Line 291 –Replace "current FDA policy" with "current FDA Guidances". Line 295-specify how a protocol is withdrawn. This reviewer agrees, supports the commenters' recommended action, and recommends that withdrawals of submitted or approved CPs be reported in the firms' Annual Review.	"Policy" is an overbroad term not restricted to CMC issues. "Policy" is the correct term because guidances are but a subset of Agency "policy." Thus, for example, if the Agency were to issue a policy that proscribed the use of stearic acid from animals sources and the sponsor's previously approved CP included the change from stearic acid from vegetable sources to stearic acid from animal sources, then, whether the CP is simply pending or has been approved, the sponsor should withdraw or modify that CP or, if pending, modify, that CP. Draft states that a protocol may be modified by a PAS submission (Part IV.E), but does not state how a protocol is withdrawn. Recommend the use of the Annual Report to withdraw protocols. To accomplish the commenters' recommendation, this reviewer would propose adding a short part (Part "**IV. F.**"): "***F. Withdrawal Of A Submitted Or Approved Comparability Protocol.*** *A sponsor may withdraw a submitted or approved comparability by submitting a "withdrawal" letter to the appropriate review division and, where appropriate, should report the accomplishment of that withdrawal in their Annual Review."*
Lines 298-312	Awkward wording; use of a decision tree or flow chart would simplify presentation. This reviewer agrees.	Is the FDA trying to state that when a the parameter in an approved protocol is changed we can get the change approved and the protocol approved in the same submission, therefore not having to get approval for both the parameter change and the protocol change separately?
Entire section V.A.2, 3 & 4	Use of a decision tree or flow chart would simplify the presentation, in particular for validation requirements of release and/or development characterization testing This reviewer agrees that the inclusion of a flow diagram and/or decision tree for each subsection might assist the reader in determining exactly what is required. However, this reviewer disagrees with part of the commenter's rationale for the adding said decision tree or flow diagram (the term "flow chart" is usually more appropriate to an outline of a computer programming proposal).	Several concepts are presented in "dense" text. This reviewer agrees with the commenters. The appropriate extent of validation information to be provided in the CMC supplement (in particular for characterization testing referenced in a comparability protocol) is unclear and may be excessive. This reviewer disagrees with the commenters' assessment concerning the "extent of validation information to be provided." It is clear what is being requested just as it is clear what **CGMP** requires in this regard. Unless the commenters' definition of "excessive" is simply "more than they want to provide," the request to provide only some of what the **CGMP** regulations require the firm to have gathered and maintained is certainly not excessive.

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
Line 455	The first sentence states that" . . .use of an approved comparability protocol may justify a reduction in reporting category." Although the FDA intent that a protocol does not automatically result in a reduced reporting category is understood, this reduced regulatory burden is a primary motivator to the effort of submitting a comparability protocol for approval.	Most sponsors would probably not go to the trouble of preparing a comparability protocol if they would not get a reduction in reporting category. This reviewer fails to see the point of these comments – they simply state the general reality. Since preparing a comparability protocol is optional, each firm has the option of not preparing one, regardless of the reason.
Lines 468	Equivalence not being demonstrated using the approved comparability protocol	Same point as line # 455. If equivalence isn't demonstrated, why refer to the protocol? Most sponsors would merely submit a "standard" PAS and request approval based on the included data (with justification). Apparently, the commenters have gotten the proverbial cart before the horse, the request is what the sponsor plans to do in the event of failure before making the change – not what the sponsor does after the problem has occurred. There is nothing to prevent the sponsor from electing to do as the commenters suggest after the fact. However, if this reviewer were reviewing a CP for acceptance and approval, this is one area where this reviewer would use the sponsor's contingency plans to assess how well they do understand their process and the probable change effects.

Minor Comments

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
General comment	Overall format	Parts V, B-G should have their own section title (section VI for example) "Specific Protocol Issues" V. H & I should also be a separate section (section VII for example) "Additional Issues for Comparability Protocols on Master Files" (for example). This reviewer suggests that the Agency consider the commenters' proposals, but would suggest the last proposed title be changed to "Issues Specific To Comparability Protocols For Materials Controlled By Drug/Veterinary Master Files."
General comment	Overall format	Shorter section titles would be more beneficial and easier to scan and use, rather than long question-type titles.
Line 24, To 2	Use of the same term "product" to mean anything from drug substance starting material to finished drug product allows for excessive ambiguity in later parts of the Draft. For example: in lines 40-41 and lines 98-99, GMP-type characteristics appear to apply to drug products only; it is unclear if lines 476-520 refer mainly to biological drug substances or also to the products made from them, and how the SUPAC Guidances (drug product processing) would be applied	In parts of the Draft in which the FDA recommendations might apply to more than one component, more specific verbiage to specify drug substance, intermediates or drug product should be used. While this reviewer understands the commenters' remarks, the reviewer has no problem with the Draft when the term product is used to mean either the drug substance or the drug product. Further, the reviewer found no instance in the Draft guidance where the term "product" could be taken to mean a non-commercial intermediates. However, to clarify the guidance, their reviewer would again recommend changing **Footnote 2** to read: "[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." In addition, using the term "product" reduces the need to repeat text that could apply to both and, as the commenters' remarks indicate, the ambiguity seems to be contrived. Therefore, his reviewer would leave it up to the Agency to decide where, if at all, the wording of text needs to be changed to restrict the "product" remarks to "drug substance, "drug product," or "drug substance and drug product."
Lines 33-34	FDA Draft notes that "should" (in the text) indicates an Agency recommendation, rather than a requirement. Please add a clarification indicating the wording that will be used for required elements.	Clarification of required elements "must" vs. "should" vs. "may" This reviewer disagrees with the commenters' statements. The requested clarification is inappropriate in a guidance document. Guidance documents do not and should not set requirements. Guidance simply provides the Agency's thinking on one way that the regulated industry can meet the requirements set forth in the **FDC Act** and the **CGMP** and other applicable regulations regulating the conduct of the pharmaceutical industry.

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
Lines 127-143	Additional FDA or ICH Guidances addressing dissolution testing, impurity comparisons and bioequivalence should be cited.	CMC elements such as comparative dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Therefore, other Guidance recommendations concerning "demonstrating equivalence" should be provided This reviewer only partly agrees with the commenters' remarks. This reviewer concurs with the referencing of other applicable **FDA** guidances but would recommend that this guidance explicitly include/request: **1.** The appropriate sections of the **CGMP** regulations contained in **21 CFR Parts 210** through **226**. **2.** For valid comparisons of drug product units, the minimum inspection plans set forth in **ISO 3951** or its American equivalent **Z 1.9**. **3.** For valid comparisons of drug substances and other non-discrete materials, inspection plans that provide proof that: **a.** The samples sampled and tested are batch representative **b.** The samples sampled are of sufficient size and properly handled in a manner that the sponsor establishes ensure that they are batch representative and each is of sufficient size to provide 10 times the amount needed for all chemical testing or, when physical properties testing is required, five times the size required for all physical tests. **c.** The sample aliquots used for each chemical test are unbiased by the subsampling procedures used and not significantly larger than the size of the dosage unit. This reviewer is opposed to referencing any ICH guidance that is not been explicitly adopted by the **FDA** and issued as an **FDA** "equivalent." In addition, this reviewer is opposed to any guidance that does not recognize the requirements of the Federal Food, Drug and Cosmetic Act (**21 U.S.C. Title 9**, the "**FDC Act**"), the current good manufacturing practice ("**CGMP**") regulations in **21 CFR Parts 210** through **226**, and the applicable recognized standards and principles of sound science. The listed items are minimums that should be given to industry to assist them in developing the scientifically sound data sets and "Comparability Protocols" based thereon that these commenters claimed the industry is interested in doing in their general comments. The listed items are also the minimums that should be given to all **FDA** personnel that are involved in any aspect of the **FDA**'s review and inspection processes.

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
Line 183; Lines 211-213	The two passages seem contradictory; please clarify This reviewer agrees with the commenters that the two statements **appear** contradictory. However, in the context stated there is no conflict. **Line 183** simply lists one factor, "The effect on safety of changes in the impurities," that the applicant should consider when developing a comparability protocol (CP). **Lines 211** through **213** state a "general" impediment, "A CMC change that requires efficacy, safety (clinical or nonclinical) studies, or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities)," that the Agency sees to using the CP approach. **Lines 215** through **217**, provide the possibility for the sponsor to overcome the impediment when it states, "It may be possible to design a comparability protocol for some of these CMC changes, but FDA may be limited in its ability to designate a reporting category other than PAS for changes implemented under such a protocol." Since this reviewer knows that safety must be an overriding consideration in all cases, this reviewer would change **Line 183** to "The effect on safety of changes ~~in the impurities~~" and **Lines 211—213** to read: "A CMC change that requires efficacy, safety (clinical or nonclinical) studies needed for new impurities, or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities)." [**Note:** The preceding change is needed to permit comparability protocols when the change only affects the level of the existing known impurities but, in general, proscribe this approach when any new impurity emerges.]	The Draft appears to be stating that a change in impurities requiring a safety evaluation might or might not be amenable to a CMC Comparability Protocol The commenters' remark is correct, *when taken out of their contexts*, the two passages seem to be contradictory. In their contexts, the passages cited by the commenters are obviously non-contradictory. However, to ensure that all comparability protocols explicitly consider safety, this reviewer would recommend removing the "in the impurities" restriction from **Line 183**. In addition, this reviewer would restrict comparability protocols to only when no new impurities are found provided the appropriate acute and short-term chronic non-clinical toxicity studies are included whenever the level of one or more impurities increases even in cases where the total level does NOT change. In this reviewer's experience, the only time that such toxicity studies would be superfluous would be the case that the change introduces no new impurities and reduces the level of all of the existing impurities. Thus, a truly improved, not simply changed, crystallization process that reduced all impurities or the addition of a recrystallization step that significantly reduces all impurities without introducing new ones would be drug substance examples where no extensive safety tests would need to be included in the protocol. However, a sponsor may want to include a simple toxicity evaluation to assess the level of improvement in the process. Finally, this reviewer would again recommend that the Agency consider includinga specific bar to the use of a comparability protocol approach unless the sponsor has established that the current process and product is fully **CGMP** compliant, the sponsor has **CGMP**-compliant data that substantiates the probable non-deleterious effect of the proposed changes and the proposed changed process has been proven to be fully **CGMP** compliant. Thus, a comparability protocol that proposed to drop a **CGMP**-mandated in-process control should be proscribed. However, one that proposed to change the test or reduce the number of samples from that required in the current **FDA**-accepted **CGMP**-compliant process to a lesser, but still **CGMP**-compliant, number should be considered.

Location In Draft	Issues in guidance/ Reviewer's Comment	Comment/Reviewer's Remarks
Lines 238-240	The Draft notes that the cover letter for the application should state that a comparability protocol is in the submission, to properly direct review, It is unclear whether this is also the case for original NDA cover letters, which typically don't get into the specifics of what documentation is in the submission.	The administrative process and cover letter annotation for original NDAs needs clarification.
Line 368	Inclusion of stability protocol information into the comparability protocol	Cross-reference to an approved stability protocol should be adequate. Since the commenters' suggestion is already the first of the two options provided in the guidance, this reviewer agrees with what is stated. However, as the Draft states, the stability protocol information may be included in the comparability protocol
Lines 440-444	Sentence is too long, leading to confusion. This reviewer agrees with the commenters that the cited sentence is too long In general, this reviewer agrees with the commenters' proposed changes but would suggest the improvements presented in the adjacent column.	Proposed wording: The comparability protocol should identify the following information, which will be submitted to FDA at the time a post approval CMC change is implemented under the FDA-approved comparability protocol: 3. the type of data (e.g., release, long-term or accelerated stability data) 4. the amount of data (e.g., 3-months accelerated stability data). 5. the data that will be generated prior to distribution of the changed product, where appropriate (e.g., when the proposed category is a CBE30, CBE-0. or AR). This reviewer's proposed wording: "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 522-548	Since the regulatory filing requirements for the analytical changes would still apply, and the science surrounding analytical validation requirements is well documented, it is doubtful that the use of comparability protocols for analytical changes would provide significant sponsor benefit.	Time required might exceed timing of submission without approved comparability protocol, with little increased risk.
Lines 55O-557	SUPAC Guidance should be cross-referenced.	

Baxter Healthcare Corporation's Submission, Dated June 24, 2003, To Docket 03D-0061: "C-07"

[**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, "Baxter Healthcare Corporation is submitting the following comments on the draft guidance for 'Comparability Protocols-Chemistry, Manufacturing, and Controls Information' published in February 2003."

"Comment 1
Please clarify how a bundled submission approach may be used for comparability protocols associated with changes affecting multiple regulatory files? (line 95)"

The short answer is that comparability protocols (CPs) are not intended to provide a pathway for "bundling" submissions.

The intent is that, in general, CPs are intended to a) be process and product specific and b) address specific related changes in the process or its controls that the submitter has established have a high probability of producing post-change product that is comparable to the pre-change product.

"Comment 2
The draft guidance stated that if the study results do not meet the criteria specified in the approved comparability protocol then the applicant can decide not to pursue the change, or to submit a prior approval supplement. However, in cases where the deviated criteria have minimal potential to impact the product, we recommend using the reporting category that would normally apply for the type of change instead of being required to submit a prior approval supplement. (line 278)"

This reviewer cannot agree with this proposal because it attempts to convert a well-defined regulatory process into an undefined one.

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.

When 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.

In general the acceptance criteria fall into two "limit" classes.

When a higher level is better (for example, a higher purity), the acceptance criteria in a CP should be set as "not less than the currently permissible lowest level."

Conversely, when a lower level is better (for example, a toxic impurity), the acceptance criteria in a CP should be set as "not more than the currently permissible highest level.

Thus, any real excursion beyond the boundaries imposed by such criteria renders the post-change material not comparable to the pre-change material.

Moreover, neither the Agency nor the sponsor know for certain that "the deviated criteria have minimal potential to impact the" safety and efficacy of the non-comparable product.

As the L-Tryptophan case illustrates, a process change that resulted in a seemingly "slight" increase in a single trace-level impurity has translated into (and therefore can translate into) significant public safety risk.

Therefore, this reviewer recommends that the Agency reject this and all such proposals into the guidance.

"Comment 3

Per the draft guidance, modifications to approved protocols should be submitted as Prior Approval Supplements. In order to further reduce regulatory burden and streamline the submission review process, we recommend that the Agency consider using the reporting mechanism outlined in the 'Changes to an Approved NDA or ANDA' guidance document for modifications to approved protocols. (line 298)"

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.

In the cases of second and third-party mandated changes, this reviewer would propose that such be treated as CBE-30 submissions to give the Agency time to make certain that the changes proposed in the submission are only changes imposed by legally binding second or third party mandates.

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.

"Comment 4

Please clarify the intent of Lines 426-436 (revision of a drug product or drug substance specification). The statement is: "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."

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.

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.

"Comment 5

Please clarify the need to provide a copy of the DMF authorization letter from the DMF holder when the regulatory tile is reviewed for a change contained in a DMF (e.g. container resin change). We believe that a new DMF authorization letter is unnecessary if the FDA has received a DMF Letter of Authorization at the time of original filing of the application. (line 611)"

This reviewer cannot agree with the commenters' statements.

This is the case because each DMF/VMF authorization letter only permits the review of the file that exists at the point in time the letter is written and only permits the Agency to review the specific parts of the DMF that are authorized in the letter.

Thus, as this reviewer understands it, once the Agency completes the review authorized by said authorization letter, the Agency cannot, except for cause, subsequently review that DMF/VMF file without being provided with an authorizing letter from the DMF/VMF holder or, for foreign firms that have agents empowered by the holder to grant access, the holder's legally authorized agent.

This level of control is required because DMF/VMF filings are "trade secret" filings that require this high level of access restriction.

Therefore a new letter is needed for two reasons:

1. In general, a pre-existing letter cannot give permission to review documents that were not in the DMF/VMF file when the letter was issued, and
2. The "trade secret" status of "DMF/VMF" files is maintained by making each letter a restricted "one time" review privilege.

Thus, unlike other filings with the Agency, all that the Agency can routinely do with each submission is file it and keep track of it.

To review any information in such files for any reason other than "for cause" (an actual public safety or efficacy issue) requires an authorization letter.

In a "for cause" case, this reviewer thinks that the Agency might need a court order before proceeding.

PDA's Submission, Dated June 24, 2003, To Docket 03D-0061: "C-06"

[**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, "PDA is pleased to provide these comments on the Draft Guidance For Industry on Comparability Protocols- Chemistry, Manufacturing, and Controls Information. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality. The comparability protocol represents a useful mechanism for facilitating registration of certain manufacturing changes. It is our assessment that the utility of the Comparability Protocol is primarily limited to planned significant changes made to complex products (e.g. proteins and sterile products). It does not add significant value for those products and classes of changes already covered by a SUPAC document. Thus though useful, the proposed Comparability Protocol alone docs not realize the objective of FDAMA to ease the regulatory burden on registration of post-approval changes. We believe that the clarifications, modifications, and scope redefinition proposed below could make the comparability protocol a more useful tool for the industry and the FDA. Our comments were prepared by a committee of experts in this field. The committee believes that the draft guidance is an excellent step towards the development of meaningful guidance on comparability protocols. It has many excellent features already."

"The committee concluded that **the document would be more useful if:**

1. **The scope of the current draft guidance is broadened.** It is unnecessarily limited with respect to product types, in that it should include biological/biotechnological products (e.g., specified biotech products). With the consolidation of biotech products into the Center for Drug Evaluation and Research, an opportunity now exists for meaningful harmonizing of regulatory mechanisms. This document represents an excellent opportunity for such harmonizing. Further, the concepts presented in this document also generally apply to biotech products."

This reviewer does <u>not</u> agree with what the commenters have stated.

First of all, this reviewer notes that this Draft does, contrary to the blanket assertion of the commenters, already permit such "biological/biotechnological products" to be addressed in a comparability protocol "**except for applications for protein products**" (**Line 24**).

Based on this, this reviewer would defer to the **FDA** and, recognizing the unique problems that establishing the comparability of protein products presents, would recommend that the text remain as it is.

"2. **Explicit guidance is provided in the document for companies that want to include planned changes in the initial NDA/BLA submissions.** Companies often need to optimize manufacturing processes soon after approval of the NDA/BLA approval. Changes to a drug product or active pharmaceutical ingredient's manufacturing process serve a variety of useful purposes, such as quality improvement, waste reduction, efficiency enhancement, etc. The ability to reasonably predict the process will significantly improve implementation by providing a predictable timeline for successful implementation. Based on the criteria for "When Might a Comparability Protocol Be Useful for a CMC Change" described in Section IIIB., we suggest inclusion of a section that discusses the submission of the

comparability protocol in the initial (new) submission. It could provide information regarding impact on the review cycle, location of the information in the Common Technical Document, and the mechanisms for changes to approve a Comparability Protocol after the initial submission."

In general, this reviewer agrees with the commenters' remarks up to the point where it states, "the mechanisms for changes to approve a Comparability Protocol after the initial submission."

This statement is problematic because, as written, it is illogical.

What do the commenters mean by "mechanisms for changes to approve a Comparability Protocol ..."?

At best, this reviewer would suggest changing the commenters' last statement to "It could provide information regarding impact on the review cycle, location of the information in the Common Technical Document, and them echanisms for changes to ~~approve~~ a Comparability Protocol after ~~the~~ its initial submission in the CMC section of an ANDA or NDA filing for a new drug."

Provided the suggested changes are made, this reviewer would support the commenters' recommendations in **Point 2**.

"3. **The ability to "bundle" the same or related changes for one or multiple products is explicitly provided.** We concur with the agency decision NOT to include provision for general protocols for multiple unrelated changes to a single product. However, the guidance should explicitly allow for making the same or related changes to multiple products, i.e., bundling, which should be applied for changes affecting multiple regulatory files. In such cases, the precedent for "bundling" multiple submissions together is well established. Examples include changing multiple solid oral products to a new packaging system (e.g., from one HDPE bottle to another HDPE bottle) or making a change to allow technology-specific multiple-product changes (e.g., new bottle for several solid orals)."

This reviewer has problems with the glib language used that presents a simple example that has little to do with what they are seeking to get the Agency to buy into.

Moreover, the commenters' remarks ignore the following realities:

1. If the commenters' goal is simply to obtain agreement on a single change (as the example states) impacting multiple products, all they need do is file a set of comparability protocols (CPs), one for each product, as a group.

2. Comparability protocols (CPs) are <u>not</u> intended to provide a pathway for "bundling" submissions. The intent is that, in general, CPs are intended to a) be process and product specific and b) address specific related changes in the process or its controls that the submitter has established have a high probability of producing post-change product that is comparable to the pre-change product.

3. If the preceding were to be allowed, a failure in one case would require the Agency to reject all changes. This is the case because all would be in one CP and require a PAS be initiated. Thus, a failure in one product in a multiple-product comparability protocol would, *at a minimum*, trigger the PAS reporting requirement for all products in such protocols because their reporting status is tied to the protocol and not to the individual

products in a multiple-product comparability protocol. How is this a good idea?

4. Allowing such "bundling" would complicate the review of the change for each product and would adversely impact the review and decision making process for the group.

Thus, the Agency should, in general, reject comparability protocols that seek to make multiple "related" changes in multiple products because of **a)** the ambiguities in review and review timeframes that such situations cause and **b)** the very real reality that a failure in any one product fails the entire set of products in the protocol.

"4. **Information related to Drug Master Filings (DMF) is included**. The use of a Comparability Protocol when a DMF is involved should be described."

This reviewer disagrees with the commenters' proposal because the use of a DMF or VMF is the same as the use in all other filing cases – to provide a mechanism for describing in detail and providing supporting data that the proposed changes will produce comparable product.

Nothing prohibits a DMF/VMF holder from filing a comparability proposal (CP) or, after making the changes in the CP, filing a CP report to their DMF.

However, unlike most other filings, the Agency is not permitted, on its own initiative, to do more than file all submissions.

This is the case because all such filings, including the annual report" are entitled to be and are treated as "trade secrets."

Thus, in general, the CP and the CP report are only subject inspectional review triggered by a biannual general **CGMP** audit or a "for cause" (product problem) inspection or authorized review (triggered by a drug-product manufacturer's filing of a submission accompanied by an appropriate DMF/VMF permission letter from the DMF/VMF holder or their legally authorized agent).

Thus, in general, DMF/VMF holders need no FDA pre-sanction to implement their process changes and, as long as the batch-representative test data on the product indicate that the post-change product is "comparable" to the pre-change product, ship post-change product to their customers.

This is the reason that this reviewer has long recommended that the purchasing firms include **a)** binding contractual requirements for the DMF/VMF holder to disclose "under a suitable confidentiality agreement" **all** process changes no mater how "trivial" and **b)** sufficiently rigorous physical property acceptance specification derived from those of the lots of components used in the manufacturer's filing to obtain initial product approval or license.

Based on the preceding realities, all this reviewer would recommend vis-à-vis CPs and Drug Master Files ("DMFs") is that the existing text be change to include Veterinary Master Files ("VMFs") whenever the current text addresses DMFs.

This is one reason that the Agency need to recognize the need for a robust biannual inspection program for DMF holder's sites and the pharmaceutical

industry needs to support funding this program and, perhaps, lobby for decreasing the inspection interval for such sites to annual.

"5. **Inspection timing could be coordinated through the FDA District Office at the request of the Manufacturer.** The Guidance should more clearly state whether FDA would permit a supplement in a non-prior-approval reporting category for a change to a new site that has not been inspected or does not have a satisfactory CGMP inspection, because an inspection is 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 that type of operation. This Guidance, as written, does not provide for use of such a Comparability Protocol, which requires insuring completion of a satisfactory CGMP inspection without a PA supplement. We propose language such as (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 finds the commenters' introductory sentence to be at odds with what should be done vis-à-vis a CP and inspection,

As with current fillings, the reviewing division needs to do an overview assessment before any inspectional action would be appropriate.

After all that assessment review could find that the changes are not comparable and trigger the rejection of the CP without the need of an inspection or, based on the firm's proposed site's having an acceptable compliance status for the changes proposed and an acceptable acceptance review, indicate that no inspection is needed.

Therefore, inspection timing should be coordinated through the review divisions and not directly through the "FDA District Office."

Moreover, to prevent the submission of "on-paper" changes or sites, the Agency should require the proposed site or sites to be fully functional and **CGMP**-compliant before a CP is submitted (as the Agency does for ANDAs and NDAs).

On the secondary issue of "site change," this reviewer recommends that the use of a CP in such cases should NOT be encouraged.

Moreover, it should be proscribed for changes to sites that have no acceptable compliance history because there are other mechanisms by which such can and should be addressed.

In addition, CPs that address proposed moves from sites directly under **FDA** review to sites that fall under a MRA or MOU should, in general, be proscribed because sites in such countries are not required to meet **CGMP** thus, by definition, any product produced in such sites cannot be "comparable" to product produced under **CGMP** (because one of the elements of comparability is that such be produced under **CGMP** not "under a quality system that is deemed to be 'comparable' to **CGMP**")

The preceding should be the case unless that "comparable" quality system establishes incoming component, in-process material and batch- or lot- release and post-release controls that meet or exceed:

- the each shipment of each lot representative sample identity testing,
- in-process representative samples of each batch at each stage (phase or step) material assessment for all critical characteristics,
- drug-product representative units' testing requirements that include the use of statistical quality control for release, and
- scientifically sound and appropriate specifications (for all factors for which the ***United States Pharmacopeia*** ("***USP***")-establishes post-release tests) that are derived (reverse engineered) from the post-release ***USP***-like "any article" specifications by the sound use of appropriate statistical procedures.

"6. **Data requirements for common changes.** Comparability Protocols would be more useful to manufacturers if FDA could provide data requirements for some common changes. Data requirements capturing the expected information for common changes such as alternate API supplier, API manufacturing site change, alternate testing laboratory, product line extension (a new fill size), expiration dating reduction or stopper changes could be very useful. We have attached three examples of such potential data requirements in Attachment 2." **(See Attachment 2**, *"Common Data Requirements for Common Changes"*)

First, because guidance does not set requirements and the guidance requests, as their examples clearly reflect the commenters understand, more than data, this reviewer would recommend to the commenters that they change their first remark to read "**Information requests for some common changes**" and frame their text in terms of the more general term "information."

Second, this reviewer agrees that detailed examples can always help the users of guidance in formulating their approach to providing the information requested in a guidance.

With the preceding in mind, this reviewer will now review the commenters' "Attachment 2."

"**Attachment 2: Data Set Requirements for Common Changes**"

"**Comparability Protocol Sample ~~Data~~ Information Requirements - #1**"

"~~New~~ A stopper fabricated from a new rubber stopper compound is being proposed as an alternate to the current approved stopper. Such a change ~~would~~ could be applicable across an entire product line. ~~The data~~ For such changes, the supporting information package should include:"

"General Information

- Specifications for the new stopper
- Material evaluation of the stopper, including USP Biological Reactivity, USP Systemic and Intracutaneous Toxicity, Cytotoxicity and USP Physiochemical tests, the identity, location and contact information for the firm or firms performing the evaluations, copies of all of the data collected, and the disposition of all lots examined;

- A supplier statement that certifies that the supplier will manufacture each lot of the new stoppers under a quality system that conforms to the applicable requirements of **CGMP**.
- The description of and specifications for each container with which the new stopper is to be used
- Copies of the methods:
  a. The supplier uses to obtain the results listed on their "Certificate of Analysis" ("COA" or "Report of Analysis" ("ROA") and the identity, location and contact for each firm that performs each evaluation listed on said certificate;
  b. The sponsor used to:
     i. Perform the required "identification" and
     ii. Validate **"the reliability of the supplier's test results"** as well as
     iii. The identity and location of the firm that did each; and
  c. The sponsor proposes to use for evaluating each batch along with the identity, location and contact information for the firm or firms that will do each evaluation.
- The sponsor's "supplier validation package" including all of the results and data obtained.
- The sponsor's "validation package for stopper evaluation" including all of the results and data obtained.
- A statement as to whether, or not, the sponsor intends to test each shipment of each lot for compliance **"with all appropriate written procedures"** (as **per 21 CFR 211.84(d)(3)**).
- If the sponsor does <u>not</u> plan to do each shipment assessment for **"for conformance with all appropriate written procedures,"** a statement of the sponsor's established elapsed-time interval for **"appropriate validation of the supplier's test results."**

<u>"Specific Information</u>

- Copies of the Certificate of Analysis for each lot of the new stopper received by the sponsor to date along with each lot's evaluation results for each evaluation performed to comply with the requirements of **21 CFR 211.84(d)(3)**, **(5)**, and **(6)**), and the disposition (accepted or rejected) of each such lot.
- At least one commercial-scale batch of drug product at the approved facility, filled and finished with the current approved commodities that includes at least one commercial-scale batch for each list number (or fill size);
- Certificate of Analysis for each such commercial-scale batch along with the data used to generate that certificate;

- Stability protocol/testing matrix; include upright and inverted vials,4 0°C & and 25°C at standard intervals as well as, if any, at any other intervals that the sponsor's protocol specifies;

- Blank batch record for each drug product list number (or fill size) for the "new stopper" lots produced for the stability study;

- Executed batch record and all data collected for each drug product list number (or fill size) for the "new stopper" lots produced for the stability study;

- Scientific report containing a minimum of three months of accelerated stability data for product produced using the new stopper as well as the historical report and data for the currently accepted stopper;

- Sterility assurance package including depyrogenation study of the proposed stopper; and

- Specifications and methods referenced in the above studies for the products produced using the currently approved stopper and, if any are different, the new stopper (if different, the rationale for changes shall be discussed and the changes justified)."

After a few changes and the appropriate additions, this reviewer agrees with the commenters' general example layout but finds that much more information should be submitted before an Agency reviewer could a) assess the *scientific soundness* of the methods, data, results, and certifications, and b) determine whether or not the new stopper is comparable to the currently accepted stopper.

Should the Agency find that this reviewer overlooked any information that should be included in the example, this reviewer would support its addition.

"Comparability Protocol Sample ~~Data~~ Information Requirements - #2"

"New API (drug substance) vendor as an alternate or replacement to the current approved vendor. Such a change ~~would~~ could be applicable across an entire product line. The ~~data~~ post-change API supporting information package for ~~an alternate~~ new vendor of a commercial FDA-accepted, approved, or licensed bulk drug should include:"

"General Information

- If the API vendor is located in a foreign country and/or the API filed under a DMF or VMF, cover Letters of Authorization from the DMF or VMF holder and, if the firm has one, its legally authorized US agent authorizing the Agency to review the comparability protocol and the rest of the DMF file and the US agent's warehousing facilities, if such exist, for any and all information bearing on the API and the API processes and process changes, including a brief description of the new API manufacturer's facility or facilities (when different sites are used to manufacture a key intermediate), GMP certification ~~letters~~, debarment certification letter (if applicable) and Central File Number.

- Copy of all of the FDA's historical and regulatorily up-to-date Establishment Inspection ~~report~~ Reports (EIRs) for the accepted API site used by the new vendor~~;.t his~~ This information may or may not be available from the new vendor. Typically, where such EIRs exist, a copy of the unexpurgated version is contained in the vendor's Type II DMF or VMF ~~or is considered~~ but, because it is proprietary in nature some vendors may be reluctant to provide this information. If not available from the vendor, the sponsor should obtain expurgated copies under Freedom of Information Act ("FOIA") and include those copies to facilitate the Agency's locating the originals. If the existing EIRs are out-of-date, do not cover the site that the vendor uses to manufacture the new API, or the proposed vendor has never been inspected, the Agency should be consulted, in general, no comparability protocol should be submitted when the vendor's site has never been inspected (such changes should be handled via the PAS approach).

- A letter from the API manufacturer that certifies that all lots of the API in question that will be offered for sale in the US and its territories is and/or will be manufactured, processed, packed, held, packaged, labeled, tested, and quality controlled under a quality system that meets the **CGMP** minimums and, *if the API manufacturer is located outside of the US*, a similar letter from the authorized US agent for the foreign API vendor. Updated facilities address and contact information that includes the new vendor's corporate and site address or addresses and contact information (names and, for each, the phone and FAX numbers as well as, if existent, e-mail address).

- Overview of the manufacture of the drug substance (including, when the pre-change and post-change vendor are the same firm or cooperating vendors, the current pre-change process versus new vendor process) with the differences explained or, when the post-change vendor does not have access to the pre-change vendor's process information, the identity, location and contact information for that vendor)."

"Specific Information

- Impurity profile comparison at ~~either~~ the drug substance ~~or drug product~~ stage for the post-change API to the pre-change API~~;~~. The data should be a side-by-side comparison of all ~~attributes~~ variable factors (or characteristics) and factor levels to demonstrate comparability. The data should demonstrate that: a) there are NO new impurities, at any level (**see Note 1**), in the post-change API, b) the level of each of the impurities in the post-change API is not significantly higher than in the pre-change API and c) the total level of impurities in the post-change API is no higher than the level in the pre-change API. ~~And equivalence of the drug substance manufactured at the two facilities;~~ Acute and short-term toxicity safety test data on the purified API and its impurity fractions should be provided to support API safety. When the API can exist in different crystalline forms, the comparison should establish that the solubility properties of the post-change API are comparable to those of the pre-change API. For a change under the control of the existing accepted vendor,

the comparison should be of ~~historical~~ pre-change API (minimum of ~~three consecutive~~ six (6) non-consecutive lots representative of the observed ranges of impurities) versus ~~new~~ the post-change API (minimum of three consecutive lots to demonstrate process reproducibility). When the post-change API is from a vendor other than the currently accepted one, the comparison should be between a minimum of three (3) consecutive lots of the new vendor's API to at least three (3) non-consecutive representative lots of the previous vendor's API (**see Note 2**). To be comparable, the post change API must have ~~quality consists of comparable~~ safety, purity, particle size distribution, polymorphic form, impurity profile and other physiochemical properties that are the same or better than the corresponding properties of the pre-change API.

[**Note 1:** If the post-change API is produced by a process that introduces impurities at any level that are not found in the pre-change API, the Comparability Protocol approach should not be used.

Note 2: When, in a new drug situation, the cooperating pre-change manufacturer of the API has not produced more than three (3) lots and does not intend to do so, the post-change vendor should submit a letter of certification from the pre-change manufacturer of the API so certifying. However, to use the Comparability Protocol Approach, the pre-change manufacturer must have produced at least two (2) lots of API.]

- ~~supplier's~~ For each post-change API batch used in any study, certified copies of a) the API manufacturer's COA and, if not in American English, certified translations thereof, b) API specifications in American English, c) the identity, location and contact information for each laboratory that is used to ensure that the API meets specification, and d) all of the data and reported information for each lot of the post-change API manufactured by the new vendor, including spectra and chromatograms as well as, if not in American English, translations of all narrative remarks.

- Analytical methods for the API including the data that establishes that each is validated, the identity, address and contact information for each facility other than the manufacturer that has done any of the testing along with the tests they have been authorized to perform, and a certification that each method will have its validity appropriately verified under actual conditions of use prior to, during, and at the end of each usage.

- Stability protocol with~~/~~ testing at standard intervals for each batch of the post-change or "new" API listed in the Comparability Protocol. The protocol should address ~~matrix: include upright and inverted;~~ a) long-term storage at "warehouse temperature" and b) an "accelerated" condition (at 30°C, 40°C, or other temperature, as appropriate).

- Stability ~~data/~~report with copies of all data as follows:

  1. When the changes are in the same process in the same facility, a 60-day accelerated stability report with lot-representative test data from the last

pre-change lot and at least three (3) post-change lots (two of which may be pilot-scale lots)
2. When the change is a move by the same firm from one site to another site, a 90-day stability report with lot-representative data from the last three (3) pre-change lots and the first three (3) post-change lots
3. When the change is the cooperative transfer of the pre-change API process from one manufacturer to a post-change API process from another manufacturer, 90-day stability report with lot-representative data for the last appropriate number and type of pre-change lots and the first three (3) post-change lots with a commitment to 180-day testing and reporting intervals for the "accelerated" testing protocols.
4. When the change is non-cooperative and/or any of the impurities in the "new" API are "new," the Comparability Protocol approach should not be used.
5. In all cases, the "warehouse storage" stability data for the 3-month's interval must be submitted for all post-change lots covered by the Comparability Protocol as a part of the commitment to carry all such through the full room-temperature stability protocol.

- Statistical analysis comparison: build this in as a requirement for New Drug Division submissions – ~~analysis of impurities, etc of historical API (minimum of three consecutive lots) versus new API (minimum of three consecutive lots).~~ since all data should be lot representative, all reporting should include the appropriate statistical analyses techniques to extrapolate from the observed data to the projected lot and process envelope of reach of the variables assessed in any data set and, where possible, such population projections should be used to establish the comparability of the APIs and API processes being compared.

First, the example was revised to limit it to the information package for the API rather than the information package for the API and the drug products made from the API.

This change was made to focus on the use of a comparability protocol solely for the API without adding the complexity required when this change is a part of a given drug-product manufacturer's decision to change API suppliers.

Though no firm manufacturers an API just to show that they can do so, most API manufacturers manufacture their API products for a variety of markets and purchasers.

Though each drug-product manufacturer who uses an API from a given source needs to perform its own comparability assessments and, if it elects to change sources or to use API or any other drug component from one of their approved vendors after that vendor changes the process for that component, these need their own comparability protocol.

In such cases, the Comparability Protocol information package described in this API Comparability Protocol outline can be embedded in their Drug-Product Comparability Protocol.

After removing the bullets addressing the drug product aspects of the changes and making the appropriate additions, this reviewer agrees with the commenters' general example layout but finds that much more information should be submitted before an Agency reviewer could a) assess the *scientific soundness* of the methods, data, results, and certifications, and b) determine whether or not the new API is comparable to the currently accepted API.

Should the Agency find that this reviewer overlooked any information that should be included in the example, this reviewer would support its addition.

"Comparability Protocol Sample ~~Data~~ Information Requirements - #3"

"Transfer of the manufacture of an approved or licensed Drug Product from the currently approved US (including Puerto Rico and all of its territories and possessions) manufacturing side to an ~~Alternate~~ alternate US manufacturing site (alternate company site~~, USA or Puerto Rico,~~ or from a US contract manufacturer to a US company site, or vice versa) ~~for the Drug Product~~. [Note: The example sample data requirements reflect a drug product that is manufactured at more than one product strength.] The data package should include:"

"General Information

- ~~Copy~~ A copy of the last three FDA's Establishment Inspection ~~report~~ reports, if they exist, and the firm's responses to any observations for the proposed new manufacturing site and~~/or~~ the firm's cGMP compliance and debarment certification letters (if the proposed site has never been inspected, a certification that the site is designed and operated in a manner that complies with all applicable **CGMP** regulations)~~;~~.
- A comparison between the proposed and the currently approved or licensed site for the facilities, equipment, the manufacturing process steps, ~~and controls section, including~~ components, ~~and compositions~~ formulations, ~~process,~~ container/closure ~~system~~ systems, labeling, packaging and labeling systems, raw material, intermediate, and drug-product handling and warehousing, and process controls, including the:

  a. Incoming components, containers and closures inspection (sampling, testing and examination) plans and established scientifically sound specifications that comply with all **CGMP** requirements and ensure that "lot shipment representative" samples are taken and appropriately inspected,
  b. In-process each-batch, batch-representative inspection plans and established scientifically sound specifications that comply with all **CGMP** requirements and ensure that "batch representative" samples are taken and appropriately inspected at the end of each stage for each variable factor whose variability may adversely affect the quality of the in-process material and the drug product, and
  c. Drug-product batch-representative inspection plans and established scientifically sound specifications that comply with all **CGMP** requirements and ensure that "batch representative" samples are taken and appropriately

inspected for each variable property that is address by the ***USP*** against their established specification as well as against the appropriate batch statistical quality control acceptance quality limits set in compliance with **21 CFR 211/165(d)**.

- ~~Microbiology:~~ The cleaning, microbiology, and sterility assurance ~~package;~~ systems used in the proposed facility to ensure the that the drug products meet their applicable standards of cleanliness and/or sterility, including, as appropriate, limits on total bioload, freedom from objectionable organisms, and sterility.
- A copy of the test and examination methods including the data that establish the methods used are valid and a statement that, at a minimum, each is verified as suitable for use under conditions of actual use at the beginning and end of each usage.
- A copy of the justifications used to establish the validity of all incoming, in-process, and drug product acceptance plans, including the validity of each of the firm's test and examination specifications.
- Commercial stability study commitment: to put the first three commercial batches for each product strength in a stability test program utilizing the approved marketed product stability protocol;.
- ~~Expiration~~ A statement of the expiration date proposed for the proposed site drug product.
- ~~Labeling: revise~~ Proposed revision of the labeling to correctly reflect "Manufactured for XXX, City, State, ZIP Code, USA" or "Manufactured by XXX, City, State, ZIP Code, USA."

"Specific Information

- Blank master batch records for each proposed strength of drug product.;
- Executed batch records for each batch produced in support of the change and all supporting logs, records, investigations and other documentation and incoming and in-process data appertaining thereto. [At a minimum, three (pilot) batch records for ~~the lowest product strength and three (pilot) batch records for the highest~~ each product strength;.]
- Certificates of Analysis for each lot of finished drug product produced in support of the comparability protocol and all of the supporting records and data appertaining thereto.
- Stability data, records, and supporting information ~~of~~ for the finished dosage form:. [a A bracketing approach can be utilized for the stability studies. Three (pilot) batches of the lowest product strength, one (1) batch of each intermediate product strength, and three (pilot) batches of the highest product strength should be manufactured and placed on stability (e.g., for finished packaged solids: long-term studies under the lesser of the labeled storage conditions or 30°C/60% RH and short-term accelerated studies at 40°C/95 % RH or, if the drug product is unstable at °C, 30°C/95% RH, and for finished packaged liquids: long-term studies under the lesser of the labeled storage conditions or 25 °C/95%RH and short-term accelerated studies at 40°C/30 %

RH or, if the drug product is unstable at 40°C, 30°C/40% RH) in the standard container orientations at standard intervals~~;~~.]

- At a minimum, the comparability protocol should provide a comparison of the first three (3) months of the accelerated and the three-month's "long-term" stability data ~~of~~ for the drug product from the current approved facility and the same data from the pilot batches produced at the proposed new manufacturing

After making some changes, this reviewer agrees with the commenters' general example layout but finds that much more information should be submitted before an Agency reviewer could a) assess the *scientific soundness* of the methods, data, results, and certifications, and b) determine whether or not the process-and product- representative data from the new drug product is comparable to the process- and product-representative data from the currently approved or licensed drug product.

Should the Agency find that this reviewer overlooked any information that should be included in the example, this reviewer would support its addition.

Having addressed the examples provided by the commenters in their "Attachment 2," this reviewer will now address the commenters other remarks.

"More specific comments are in the attachment." (**See Attachment**, *"PDA comments on the FDA Draft Guidance for Industry on Comparability Protocols- Chemistry, Manufacturing, and Controls Information"*)

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
II. Line 90	Please clarify how comparability protocols can be applied for changes affecting multiple regulatory files, such as a change to a container/closure system. Can the change be filed via a bundled submission route?	An underlying principle endorsed by this document is that a change must be product specific. We disagree. The greatest utility and, therefore, reduction of regulatory burden, would occur if appropriate application to multiple applications is provided. Frequently, for example, a change to a container/closure system, a raw material change, or excipient change is made to several products at one time. The ability to "bundle" comparability protocols is necessary for companies to efficiently incorporate such changes without undue constraints while confirming that product continues to meet the agreed standards. For all of the reasons stated in the general comments, thisr eviewer doesn_ot, in general, agree with "bundling" unless the changes are for a single drug product *except for the case of multiple strengths of the same drug product dosage form.*

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
II. A. Line 98	Grammatical change to: "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 as these factors relate to the safety and effectiveness of the product." (change in bold) for clarification.	Typographical error: "in" should be "on". This reviewer agrees with this change.
II. B. Lines 107-109	Clarify footnote 5 to indicate how the reduced reporting category is ensured and how the agreement between the agency and the applicant is reached.	The general reference to the "agreed" reporting category should be further clarified in the text of the document. How will this agreement be reached? What happens if the company disagrees with the FDA position? What recourse is available to the Manufacturer if there is a desire to appeal/challenge an FDA decision?
II. B. Lines 109-111	Change from: "Furthermore, because a detailed plan will be provided in the comparability protocol, the FDA is less likely to request additional information to support changes made under the protocol (see 1V.D for a potential exception)." Change sentence to: "Furthermore, because a detailed plan will be submitted in the comparability protocol, FDA has the opportunity to provide input earlier in the change process and is less likely to request additional information to support changes made under the protocol (see 1V.D for a potential exception)."	When using a Comparability Protocol, the applicant benefits by receiving FDA's comments regarding the change and assessing the effects of the change earlier in the process than would occur without the use of a Comparability Protocol.
II. D. Line 143	Add a bullet for BAC-PAC	Include reference for "BAC-PAC (Bulk Actives Post Approval Changes)" since it is applicable to this guidance. This reviewer agrees that BACPAC should be referenced as prior guidance that was the FDA's best thinking at the time that guidance was released. However, when the BACPAC guidance and this guidance appear to have a conflict, the text in this guidance should be considered as superseding that of BACPAC. This is the case because BACPAC is a prior guidance – representing what <u>was</u> the Agency's best thinking at that time.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
III. A. Line 152	Change from: 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. Change to: Using the information submitted by the manufacturer, FDA will be able to determine if the change submitted under an approved Comparability Protocol will reduce the reporting/review requirements for the change submitted without an approved comparability protocol. Also, where multiple changes are included, the agency will be able to provide information on each of the specific changes.	Clarification is needed in this sentence if determination of category for filing will be identified Comparability Protocols will be most useful if FDA declares the filing category for each proposed change covered. While this reviewer agrees with the first sentence of the commenter's recommended change in the text, this reviewer does not agree with yet another of the commenters' attempt to enlarge the guidance beyond its proposed bounds as embodied in the sentence they attempt to add. Based on the preceding, this reviewer would recommend the commenters' proposed change be revised to: "Using the information and data submitted by the manufacturer, ~~FDA~~ the Agency will be able to determine if the ~~change~~ proposed changes submitted ~~under an approved~~ in a Comparability Protocol will reduce the reporting~~/~~ and/or review requirements ~~for~~ vis-à-vis the ~~change~~ changes submitted ~~without an approved~~ via an Agency-acceptable filing that lacks a comparability protocol. ~~Also, where multiple changes are included, the agency will be able to provide information on each of the specific changes.~~" The Agency's responsibility should be to judge the comparability protocol (CP) as a whole and to base their decision on that whole. If, in the Agency's review, a particular change is identified as being problematic that information should be included in the Agency's initial assessment communication. However, to preclude non-productive "nit picking" and minimize the burden on the reviewers, the Agency should not specifically address each and every change in their assessment responses. It is and should be the sponsor's responsibility to assess the probable regulatory impact for each of the changes in a CP that they choose to incorporate in a given CP.
III. A. Lines 154-156	Change from: "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)." Change 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 CBE30 to CBE; or from CBE to AR)."	The current example is confusing. Going from a PAS to CBE30 to CBE to an AR would normally be considered a three-category reduction. This reviewer agrees with the commenters' revision of the text. It does clear up the confusion that the Draft text has apparently engendered.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
III. A. Lines 156-157	In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR).	Please provide an example of when a reduction of more than one category is possible. This reviewer supports the commenters' request. A good example or two can be very helpful.
III. B. Lines 162-238	General Concept for the Section	The guidance does not address the use of a Comparability Protocol when identical changes are made to multiple products and are submitted to FDA in a "bundled" form. Please reconsider expanding the use of the Comparability Protocol concept to allow a bundled submission for multiple product related changes, such as packaging. This will especially useful for repetitive changes. In general, this reviewer is opposed to "bundling" for the reasons cited in this reviewer's remarks to that issue in the commenters' "General Comments." In cases where a single change not only affects multiple products but also the existing information and data clearly indicate that the change will have the same "no adverse" effect on all of the products would recommend submitting a group of CPs – not a single CP into which all have been bundled. Given the existence of today's sophisticated word processors and databases, the "grouped" submission approach could, if properly implemented, provide all of the alleged benefits of "bundling" without the downside risks that "bundling" presents. With today's information management systems, the *de minimus* overhead added by the "grouped" approach would be more than offset by the negative impacts that a single failure for one o the submitted changes would cause for a "bundled" CP. Moreover, this approach would provide the Agency with added review flexibility.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
III. B. Lines 163-164	Current: "However, we recommend that each change be discrete and specific". Proposed: The use of the Comparability Protocol for technology specific changes (e.g., change in filtration process) which broadly applies to multiple products is also appropriate. The need for each change to be discrete and specific is obvious. A proposed change should not change a pH limit from 'not more than 4.0' to 'not more than 3.5 to 4.5.' – a limit should be a discrete number. Similarly, one should not propose changing a process that states 'add 200 L of 1 N aqueous acetic acid' to one that says 'add 200 L of a suitable 1 N acid solution' – a change should be specific. With respect to "technology specific changes," let us consider the two examples, the one in the commenter's "... Recommendation ..." column and the other in their "... regarding text" column. Obviously, changing a filtration process to a new one that improves the "quality" of the filtrate containing the active in Process "A" could adversely impact the "quality" of the filter cake containing the active in Process "B" The second example, "new bottle for several oral solids," is more of an item change than a technology change. Similar caveats apply in that the protective effect of the new bottle may not be the same for all of the different "oral solids" to which it is proposed to be applied.	Wording should be broadened to allow technology-specific, multiple product changes (e.g., new bottle for several products). This reviewer cannot agree with the changes that the commenters are proposing because, *regardless of the number of changes*, each change should, as the draft text states, "**be discrete and specific.**" In addition, the commenters' remarks are <u>not</u> even self-consistent. The first example ("Proposed:") speaks to technology specific changes applied to multiple products while the second ("new bottle") speaks to multiple related changes in a comparability protocol. Changing the example filtration process to a different filtration process might affect different processes differently and, for that reason, should not be proposed in a blanket protocol, as the commenters would suggest. Further, the commenters' example did <u>not</u> even suggest that such be limited to cases where the proposed filtration process change is known to improvethe quality of the desired fraction (filtrate or filter cake). Moreover, *though current technology exists to make plastic bottles impervious to the diffusion of deleterious gases (such as water vapor, oxygen, carbon monoxide and dioxide, and nitrous and nitric oxides) and light,* **few fir m seem willing to adopt such bottles because of their costs.** The industry seems to prefer instead to use overwraps and adsorbents to "control" or "mitigate" the problems.
III. C. Lines 224 – 226	Change the bullet from: "A change from plant. Animal. Or multicellular (e.g., algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal)" Change the bullet to include bolded text: "A change from plant, animal, or multicellular (e.g., algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal), **depending on the extent of the purification process.**	Even if the downstream purification process is extensive, it should be possible to handle such a change under a comparability protocol This reviewer again opposes adding the commenters' phrase. In the context in which this text appears, the modifying clause is <u>not</u> only superfluous but also introduces unneeded ambiguity. The bullets are "**Specific examples of changes that may be difficult to justify under a comparability protocol can include**" – difficult but not impossible. Therefore, this bullet does <u>not</u> warrant the "it depends" ambiguity that the commenters are seeking to introduce.

Section ID &Line #	Comment Recommendation for Revision	Comments regarding text
III. C. **Line 227**	Change the bullet from: "A change from synthesis-derived to naturally sourced material and vice versa" Change the bullet to include bolded text: A change from synthesis-derived to naturally sourced material and vice versa, **depending on the extent of the purification process"**	Even if the downstream purification process is extensive, it should be possible to handle such a change under a comparability protocol In the context in which this text appears, the modifying clause is not only superfluous but also introduces unneeded ambiguity. The bullets are **"Specific examples of changes that may be difficult to justify under a comparability protocol can include."** Therefore, this bullet does not warrant the "it depends" ambiguity that the commenters are seeking to introduce.
III. C. **Lines 229-231**	Delete lines 229 – 231 as currently stated: A move to a manufacturing site, facility, or area when a prior approval supplement is recommended because a current good manufacturing practice (CGMP) inspection is warranted (e.g., see examples in guidances listed in II.D.) Insert a new paragraph: "When a Manufacturer moves a process to a previously uninspected manufacturing facility, the approval of the Comparability Protocol signifies that the Manufacturer should notify the field when the facility is ready for inspection status. The inspection should be scheduled prior to the submission of the agreed data package to the review division. Upon receipt of the acceptable GMP status from the Field, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol." In context, this reviewer again opposes making the commenter's suggested changes. Moreover, the proposed paragraph speaks of a condition that may be contrary to reality, "the approval of the Comparability Protocol," and what this approval "signifies." The commenters' proposed text ignores the reality that the protocol may be rejected and, in such cases, the existence of a submitted Comparability Protocol is of no significance. Further, the commenters', "Upon receipt of the acceptable GMP status, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol," misidentifies the standard required of the facility as "acceptable GMP status" when the **FDC Act** and the **CGMP** regulations require the site to be found to be "fully **CGMP** compliant" before any product may be even offered for sale.	If a CGMP inspection is warranted for a manufacturing site, facility, or area, it is not clear why the Comparability Protocol could not be submitted for the site change, and used to trigger the inspection. After the PAI and Comparability Protocol approval, the site change could be reported at the reduced reporting category without the need for the increased regulatory time constraints for implementation. Distribution of product would not be allowed prior to the receipt of the acceptable GMP status. As written, this represents a significant increase in the regulatory burden that is contrary to the spirit of the Prescription Drug User Fee Act. Though commenters phrase the question so elegantly, they attempt to confuse the realities that they pose as an implied "why" question. If, as they initially state, a Comparability Protocol would in this case require a PAS, then why do they state, in their second remark, "the site change could be reported at the reduced reporting category" when, if their initial statement is true, their second statement is, at best, illogical. Moreover, their attempt to use the false logic that "if A requires C and B requires C, then A and B are a priori equivalent." Finally, they fail to answer their own question – the obvious answer is that the Agency sees that such approaches should not be allowed. Moreover, the text does allow for the possibility that such a Comparability Protocol may be allowed in some cases (**Lines 217** and **218**, **"Specific examples of changes that may be difficult to justify under a comparability protocol can include."** In the context in which this text appears, the text should be kept as it is and the proposed paragraph has no place. The bullets are **"Specific examples of changes that may be difficult to justify under a comparability protocol can include."** Therefore, the proposed changes are both unwarranted and misplaced.