

# Paul G King Consulting/FAME SYSTEMS

Comments on Draft "CMC" Document \\CDS029\CDERGUID\5427dft.doc of 02/13/03

Friday, 9 May 2003

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

**RE: Docket No. 03D-0061**

## FORMAL COMMENTS ON:

**Docket Number** : 03D-0061

**Comments On** : "Draft Guidance for Industry on Comparability Protocols — Chemistry, Manufacturing, and Controls Information"<sup>1</sup>

Pursuant to a "request for comments" promulgated in *FEDERAL REGISTER*, **68(37)**, pages 8772 – 8773, Tuesday, 25 February 2003

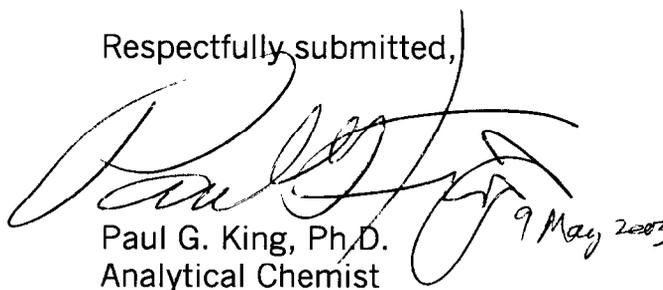
The comments being provided to Docket: "03D-0061" are based on a second reading and review of " **Draft Guidance for Industry on Comparability Protocols — Chemistry, Manufacturing, and Controls Information** [\\CDS029\CDERGUID\5427dft.doc - 02/13/03]" that attempts to add elements that connect various issues in the draft provided by the Agency to the CGMP regulations upon which they are supposed to be based.

The current comments embody slight revisions and grammatical corrections from the original comments submitted earlier (posted on 5 May 2003).

In general, changes from the original posting are highlighted in blue.

Should anyone in the Agency who reviews said comments need clarification on a given suggestion, then they should e-mail me (**drking at dr-king.com**) their observation and, where possible, I will provide appropriate clarifying remarks.

Respectfully submitted,



Paul G. King, Ph.D.  
Analytical Chemist

03D-0061

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<sup>1</sup> For questions regarding this draft document contact Stephen Moore (CDER) 301-827-6430, Chris Joneckis (CBER) 301-435-5681, or Dennis Bensley (CVM) 301-827-6956.

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Comments on Draft "CMC" Document \\CDS029\CDERGUID\5427dft.doc of 02/13/03

## Introduction

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

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

To facilitate differentiation between the proposed alternative and the **FDA's** Draft, the changes will be in Lydian or highlighted Lydian font and the **FDA** draft will be in the Perpetua font.

With the preceding in mind, let us proceed to review the proposed draft.

## Comments

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

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Comments on Draft "CMC" Document \\CDS029\CDERGUID\5427dft.doc of 02/13/03

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127-135	<p><b>D. Where Can More Information on Post-approval Changes and Demonstration of Equivalence Be Found?</b></p> <p>This guidance, once finalized, is not intended to supersede the applicable CGMP regulations governing drugs and drug products or other FDA guidance documents, rather it supplements them with information on using comparability protocols to implement post-approval CMC changes. We recommend that applicants consult the CGMP regulations for compliance first and then all relevant guidances<sup>1</sup> for information relating to postapproval changes. The following guidances provide especially relevant information on (1) demonstrating equivalence, (2) documentation to be provided to support post-approval changes, and (3) the recommended reporting categories.</p>	<p><b>D. Where Can More Information on Postapproval Changes and Demonstration of Equivalence Be Found?</b></p> <p>This guidance, once finalized, is not intended to supersede other FDA guidance documents, rather it supplements them with information on using comparability protocols to implement postapproval CMC changes. We recommend that applicants consult all relevant guidances<sup>2</sup> for information relating to postapproval changes. The following guidances provide especially relevant information on (1) demonstrating equivalence, (2) documentation to be provided to support postapproval changes, and (3) the recommended reporting categories.</p>
165-170	<p>We recommend that you have sufficient <b>process-representative</b> manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and <b>the scientifically sound and appropriate CGMP-compliant</b> acceptance criteria appropriate for demonstrating that the CMC change or changes <b>will still fully comply with all of the applicable CGMP requirements, are based on recognized standards and sound science, and will not adversely affect</b> the product.</p>	<p>We recommend that you have sufficient manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and acceptance criteria appropriate for demonstrating that the CMC change or changes will not adversely affect the product.</p>
173-175	<p>We recommend you consider product-specific and process-specific <b>characteristics</b> when determining whether to develop a comparability protocol. <b>Characteristics</b> can include, but are not limited to, the following:</p> <p>(The use of the word "<b>attribute</b>" should be restricted to those "<b>characteristics</b>" that may be <b>inspected</b> by <i>sampling</i> and <i>examination or classification</i> to be consistent with the recognized American scientific inspection standard ANSI Z 1.4. Similarly, characteristics that are sampled and tested for a level should be called "factors" to be consistent with ANSI Z 1.9, the recognized standard governing such inspections.)</p>	<p>We recommend you consider product-specific and process-specific attributes when determining whether to develop a comparability protocol. Attributes can include, but are not limited to, the following:</p>

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9 May 2003

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190-194	<p>In general, <del>we recommend that</del> a comparability protocol should be considered only if the product resulting from the changes is expected to meet <b>all the requisite CGMP-compliant</b>, approved drug substance, <b>in-process</b>, and/or drug product specifications <b>for each batch</b> and appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for <b>non-routine</b> tests such as characterization studies) to detect <b>and assess</b> the effect, <b>if any</b>, of the change on the approved product.</p>	<p>In general, we recommend that a comparability protocol be considered only if the product resulting from the changes is expected to meet the approved drug substance and/or drug product specifications and appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for nonroutine tests such as characterization studies) to detect the effect of the change on the approved product.</p>
<p>Between lines 232 and 233</p>	<p><b>D. When Is a Comparability Protocol Proscribed?</b></p> <p>A comparability protocol is proscribed whenever the proposed CMC changes do not meet the requirements established in the applicable CGMP regulations governing the process or product for which a firm is considering such CMC changes. Thus, before considering any CMC changes, the firm should ensure that said CMC changes collectively, and individually, do not conflict with any applicable CGMP requirement.</p>	
255-259	<p>Furthermore, an applicant who is using an approved comparability protocol to implement <b>post-approval</b> CMC changes must assess the effect of the changes on the identity, strength, quality (<b>including, but not limited to, the batch uniformity of the active or actives in the dosage units and their release from the dosage units</b>), 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.)*</p>	<p>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)).</p>
278-281	<p>If you decide to pursue the change, you should submit a prior approval supplement that provides supporting data <b>from a statistically sufficient number of batch-representative units</b> to justify why the change will not adversely affect the identity, strength, quality (<b>including, but not limited to, the batch uniformity of the active or actives in the dosage units and their release from the dosage units</b>), purity, and potency of the specific drug product as these factors relate to the safety and effectiveness of the product.</p>	<p>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.</p>
288-290	<p>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 <b>the applicable CGMP requirements</b>, approved application, and current FDA policy.</p>	<p>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.</p>

*Paul King*  
9/11/03

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

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

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

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406-414	<p>However, if these analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure <b>should</b> be provided <b>whenever</b> a <b>post-approval CMC</b> change implemented using the approved comparability protocol is reported to FDA.</p> <p>In cases where changes in analytical procedures are intended to be implemented independent of other CMC changes, we recommend that a comparability protocol specific for analytical procedure changes <b>should</b> be submitted (see V.C)</p>	<p>However, if these analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.</p> <p>In cases where changes in analytical procedures are intended to be implemented independent of other CMC changes, we recommend that a comparability protocol specific for analytical procedure changes be submitted (see V.C)</p>
418-423	<p><b>4. Acceptance Criteria</b></p> <p>You should include the <i>scientifically sound and appropriate, statistics-based</i> acceptance criteria (numerical limits, ranges or other criteria) <b>and their scientific justification</b> 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 <b>post-</b> change material. In general, the drug substance and drug product specification <b>should</b> be <b>CGMP-compliant and identical to, or within, the specification limit, range or other criteria contained</b> in the approved application. Any statistical analyses, <i>including those required by 21 CFR 211.165(d) for the drug product</i>, that will be performed and the associated evaluation criteria <b>should</b> be identified.</p> <p>[Note: If a firm's current approved drug-product application does not comply with the requirements set forth in 21 CFR 211, then that deficiency should be corrected before any other comparability protocol is submitted.]</p>	<p><b>4. Acceptance Criteria</b></p> <p>You should include the acceptance criteria (numerical limits, ranges or other criteria) for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and postchange material. In general, the drug substance and drug product specification would be identical to that in the approved application. Any statistical analyses that will be performed and the associated evaluation criteria would be identified.</p>

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9/16/2003

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Comments on Draft "CMC" Document \\CDS029\CDERGUID\5427dft.doc of 02/13/03

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425-435	<p>If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the <b>designated</b> reporting category<sup>3</sup> for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol.</p> <p>When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), the change <b>should</b> be reported as recommended for the specification change.</p> <p>If the recommended reporting category for the specification change is the same <b>as</b>, or lower than, the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided to the FDA when the <b>post-approval CMC change, using an approved comparability protocol, is implemented and subsequently</b> reported to FDA.</p>	<p>If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the recommended reporting category<sup>4</sup> for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), the change would be reported as recommended for the specification change. If the recommended reporting category for the specification change is the same or lower than the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.</p>

*Reviewed  
7 May 2003*

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437-450	<p><b>5. Data to Be Reported Under or Included With the Comparability Protocol</b></p> <p>You should identify the type (e.g., <b>in-coming material, in-process material, drug-product acceptance in compliance with 21 CFR 211.165 and, where applicable, 21 CFR 211.167</b>, long-term or accelerated stability data) and the amount of data (e.g., "<b>n<sub>i</sub></b>" lot-representative samples of "<b>m<sub>i</sub></b>" incoming lots for "<b>l<sub>i</sub></b>" characteristics, "<b>n<sub>p</sub></b>" representative sample sets from "<b>m<sub>p</sub></b>" process representative evaluations of "<b>k<sub>pa</sub></b>" attribute factors and "<b>l<sub>pv</sub></b>" variable factors, "<b>n<sub>dp</sub></b>" batch-representative sample sets from "<b>m<sub>dp</sub></b>" batch evaluations of "<b>k<sub>dpa</sub></b>" attribute factors and "<b>l<sub>dpv</sub></b>" variable factors of the drug product for acceptance. 3-months accelerated process-representative stability data) that will be submitted at the time a postapproval CMC change implemented using <b>an</b> 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).</p> <p>If available, you <b>may</b> include any <b>process-representative</b> data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Data obtained from a <i>scientifically sound and appropriate</i> small-scale process or other <i>scientifically sound and appropriate</i> studies, incorporating the proposed change, <b>may be used as</b> preliminary evidence that the change is feasible, as well as provide preliminary information on the effect of the change on the product. <i>Scientifically sound and appropriate development</i> or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product.</p>	<p><b>5. Data to Be Reported Under or Included With the ... Protocol</b></p> <p>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).</p> <p>If available, you can include any data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Data obtained from a small-scale process or other studies incorporating the proposed change can provide preliminary evidence that the change is feasible, as well as preliminary information on the effect of the change on the product. Development or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product.</p>

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462-468	<p><b>7. Equivalence Not Demonstrated Using the Approved Comparability Protocol</b></p> <p>It is anticipated that some changes in the manufacturing process will result in a <b>postchange</b> drug product that: <b>a)</b> cannot be demonstrated to be equivalent to the <b>prechange</b> drug product without more extensive physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing <b>or b)</b> does not meet the <b>prespecified</b> acceptance criteria in the protocol. You should <b>include</b> in the protocol the <b>explicit</b> steps you will take <b>should either circumstance occur</b>.</p>	<p><b>7. Equivalence Not Demonstrated Using the Approved Comparability Protocol</b></p> <p>It is anticipated that some changes in the manufacturing process will result in a postchange product that cannot be demonstrated to be equivalent to the prechange product without more extensive physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or in a product that does not meet the prespecified acceptance criteria in the protocol. You should identify in the protocol the steps you will take in such circumstances.</p>
481-485	<p><b>1. Comparison of Physical Characteristics</b></p> <p>A comparability protocol <b>should</b> normally include <b>incoming material and/or in-process material inspection plans that properly compare the physical characteristics (e.g., polymorph forms, particle size distribution, density, flow, affinity) of materials that make up the product produced using the old and new processes when these characteristics are relevant to the safety and the uniformity of: a) the active or actives, b) the release of the active or actives, or c) any other key quality factors in the product that can affect its efficacy of the product when taken by the consumer.</b></p>	<p><b>1. Comparison of Physical Characteristics</b></p> <p>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.</p>

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Comments on Draft "CMC" Document \\CDS029\CDERGUID\5427dft.doc of 02/13/03

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

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9 May 2003

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

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9 May 2003

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587-592	<p><b>G. Can Implementation of or Changes in Process Analytical Technology (PAT) Be Addressed in a Comparability Protocol?</b></p> <p>FDA anticipates that implementation of or changes in PAT could be addressed in a comparability protocol. Early dialogue with FDA is encouraged. The FDA intends to publish a guidance on PAT in the future. <b>However, if the PAT intends to change from the quantitative testing of an appropriate population-representative sample set to an approach that uses training sets and the classification of an appropriate set of samples, then:</b></p> <ol style="list-style-type: none"> <li>1. Appropriately rigorous controls will be required for, and must be implemented for, all components used in the manufacture of the product.</li> <li>2. The training sets used to train the classifier will need to appropriately span all of the possible component combinations in sets that are deliberately prepared to address all of the factors (e.g., assay, release, rate of release, impurity) that the classifier is designed to assess. [Note: The number of training samples in each training required set should be several times the number of population-representative samples required for the evaluation of the product.]</li> <li>3. The typical appropriate number of representative samples that need to be classified from a typical batch of product should be based on the attribute number requirements established in ANSI Z 1.4 because classification is an attribute assessment.</li> </ol>	<p><b>G. Can Implementation of or Changes in Process Analytical Technology (PAT) Be Addressed in a Comparability Protocol?</b></p> <p>FDA anticipates that implementation of or changes in PAT could be addressed in a comparability protocol. Early dialogue with FDA is encouraged. The FDA intends to publish a guidance on PAT in the future.</p>
594-605	<p><b>H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability Protocol?</b></p> <p>A master file can be cross-referenced in a comparability protocol that provides for CMC changes (e.g., new manufacturer of drug substance, container resin). The protocol <b>should</b> include a commitment to provide a letter authorizing the FDA to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA. The comparability protocol <b>should</b> also indicate the type of information (e.g., manufacturing and formulation information for a plastic resin) that will be referenced in the master file and the information that you will provide <b>including</b> the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to approved specification, compatibility studies, stability studies).</p>	<p><b>I. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability Protocol?</b></p> <p>A master file can be cross-referenced in a comparability protocol that provides for CMC changes (e.g., new manufacturer of drug substance, container resin). The protocol would include a commitment to provide a letter authorizing the FDA to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA. The comparability protocol would also indicate the type of information (e.g., manufacturing and formulation information for a plastic resin) that will be referenced in the master file and the information that you will provide such as the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to approved specification, compatibility studies, stability studies).</p>

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7 May 2003

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Comments on Draft "CMC" Document \\CDS029\CDERGUID\5427dft.doc of 02/13/03

## Concluding Remarks

Hopefully, those who review the preceding comments will do so with an open mind and a copy of the CGMP regulations for drugs (**21 CFR 210**) and finished pharmaceuticals (**21 CFR 211**).

Hopefully, all will accept that the minimum requirements set forth in **21 CFR 211** are truly the minimum that any firm can do and have their FDA-regulated finished products be CGMP-compliant.

Hopefully, all will remember that products covered by **21 CFR 211** that are not manufactured in full compliance with **21 CFR 211** are adulterated and should not be distributed.

With the preceding in mind and remembering that the **FDA** has no authority to issue guidance that differs from any of the clear requirements set forth in **21 CFR 211**, hopefully, the **FDA** will appropriately revise their draft and issue guidance that fully complies with the clear, but seemingly overlooked, requirements of **21 CFR 211**.

*Paul King*  
9 Mar 2003