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Novartis Pharmaceuticals Corporation Comments on the FDA DRAFT Guidance "Comparability Protocols – CMC Information", Docket 03D-0061

Major comments

Line number	Issues in guidance	Comment
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) 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. Some points such as impurity qualification or dissolution evaluation include FDA groups in addition to the CMC reviewers.
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.
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 Line 295—specify how a protocol is withdrawn.	"Policy" is an overbroad term not restricted to CMC issues. Draft states that a protocol may be modified by a PAS submission (Part IV.E), but does not state how a protocol is withdrawn.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.
Lines 298-312	Awkward wording; use of a decision tree or flow chart would simplify the presentation.	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, 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	Several concepts are presented in "dense" text. The appropriate extent of validation information to be provided in the CMC supplement (in particular for characterization testing referenced in a

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		comparability protocol) is unclear and may be excessive.
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.
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).

Minor comments

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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).
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, 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. 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.
Lines 33-34	FDA Draft notes that "should" (in the text) indicates an Agency recommendation, rather than a requirement. Please add a	Clarification of required elements "must" vs. "should" vs. "may"

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	clarification indicating the wording that w ill be used for required elements.	
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
Line 183; Lines 211-213	The two passages seem contradictory; please clarify	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
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.
Lines 440-444	Sentence is too long, leading to confusion.	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: 1. the type of data (e.g., release, long-term or accelerated stability 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).
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.

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Lines 550-557	SUPAC Guidance should be cross-referenced.	