



P&GP Comments on: Draft FDA Guidance Drug Substance CMC Information

7-28-04
Procter & Gamble Pharmaceuticals
147 State Rt. 320, Woods Corners
P.O. Box 191
Norwich, NY 13815-0191
(607) 335-2111 phone
(607) 335-2064 fax
www.pg.com

June 30, 2004

Dockets Management Branch
HFA-305
Food & Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Re: **DOCKET No. 2003D-0571**. Guidance for Industry: Drug Substance, Chemistry, Manufacturing and Controls Information

We sincerely appreciate the efforts of the FDA to develop revised industry guidance for drug substance submissions CMC information and welcome the opportunity to submit our comments. This Guidance, when finalized, will contain requirements which are very relevant to our pharmaceutical products.

Our comments that follow are divided into two categories: General Comments and Suggested Line Item Changes. We realize that you will likely receive numerous comments, so P&GP comments of highest importance are **highlighted**.

General Comments

Definition of Starting Material – Honestly, we were disappointed with this section. We have followed closely the Agency’s “GMPs for the Twenty-first Century” initiative and felt that the draft guidance was a made-to-order opportunity to apply the risk- and science-based criteria in updating the 1987 Guidance. But clearly this was not done. The focus on propinquity, commercial availability (whether in the pharmaceutical or nonpharmaceutical market) and the unwillingness to recognized the value of modern analytical techniques are obvious examples from the draft guidance that seem to signal a chilling resistance on the Agency’s part to move into the next century. It is our hope that the Agency will agree to overhaul the entire section of the draft guidance on Starting Materials focusing on scientific rationale and evidence rather than on subjective and arbitrary criteria. The starting material criteria should be much more focused on the technical justification i.e. appropriate specifications, impact on the quality of the final drug substance, etc.

Furthermore we recommend that this single topic is of such critical importance to both the Agency and Industry to warrant additional open dialog before it is canonized in the formal guidance document.

Critical parameters (Section S.2.4) – The identification of critical process parameters and critical quality attributes is a sound concept that gets at the heart of quality assurance. However, the draft guidance is much too restrictive in that it does not embrace the Agency’s new mantra of moving to a greater reliance on risk assessment and science-based qualification. Given the state of analytical technology, applicants should be given the flexibility to move to a higher technical standard. Identifying and justifying critical parameters is an excellent place to start.

2003D-0571

C16



P&GP Comments on: Draft FDA Guidance Drug Substance CMC Information

Agreement with Q7A – Q7A, The ICH Quality Guidance on API GMPs, is a gold standard that is being embraced globally. Given this, it was disconcerting to read definitions in the Draft Guidance of Reprocessing, Reworking and Starting Materials that were different from Q7A. The Agency fully supported Q7A and endorsed it. For the fundamental definitions, it does not seem unreasonable to expect that they would be the same between the two documents. So long as a reliance on scientific rigor and adequate justification is presented, the definitions should be the same. This will further pave the way to better harmonization.

The suggested line item changes are provided in the attached table. Please contact me if you need further assistance or have any questions regarding these comments.

Very sincerely yours,

A handwritten signature in black ink, appearing to read 'Thomas L. Cupps', with a long, sweeping flourish extending to the right.

Thomas L. Cupps, Associate Director
Chemical Development
Procter & Gamble Pharmaceuticals

Attachment



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

ATTACHMENT: Procter & Gamble Pharmaceutical's Suggested Revisions (by line number in Draft Guidance posted on the CDER website)

Line	Item	Concerns	Proposed change
59	peptides	Confusing. Peptides can refer to proteins and smaller, synthetic peptides.	Peptides here should specifically exclude small peptides made synthetically
341		These are really drug product terms.	Delete "strength and potency." Or reword to distinguish between DS and DP.
352	biological activity	Lack of clarity	Explain what kind of information is expected for "biological activity"
377	"manufacturing responsibility"	Lack of clarity	Define manufacturing responsibility. Does this refer to what compound is made or something else?
383	"provide building number"	Too much information required that is of limited value.	Eliminate the requirement to provide building numbers in multi-building facilities. Providing reactor numbers in the batch records should suffice.
414	critical	Undefined term.	Indicate that the definition of critical is in the glossary.
422	"postsynthesis material"	Introduction of a new term that is somewhat confusing and arbitrary.	We would prefer not having to learn a whole new set of terms for this guidance. However, we would certainly welcome a more open discussion of this in order to better appreciate the Agency's concerns and reasons for its introduction.
424, 460, 504, 541, 798	"postsynthesis material"	Introduction of a new term that is somewhat confusing and arbitrary	Same
427	Operating parameters	Operating parameters is a broad category and for purposes of this section should really be limited to critical parameters.	Add the word "critical" in front of "Operating parameters."
433	Yield ranges for <u>each</u> reaction step.	Here again, what is really important are the yield ranges for critical reaction steps. This a more of a risk-based approach and better supports critical quality attributes approach	Change to "critical reaction steps."
443	"the description should identify <u>all</u> process controls	All process controls will not necessarily affect <u>critical steps</u> or process controls.	Substitute "critical" for "all"
451	". . quantities specified"	Here again, what is important is that quantities affecting critical steps or process controls be specified.	Change to read "quantities specified only if critical."
453	". . quantities specified"	Here again, what is important is that quantities affecting critical steps or process controls be specified.	Change to read "quantities specified only if critical."
489, 1526	BSE	Feel that added emphasis is needed that we are not dealing just with US sources.	Add "regardless of country of origin" after "materials"



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

508, 510, 512	Process Controls	Here again, what we urge is emphasis on critical	Insert the word "critical" at start of each bullet.
521	Process controls	Requesting too much information when asking for "all process controls, critical or otherwise." All that is really needed are critical process controls.	Reword to say, "All critical process controls . . ."
524-36	Examples of critical.	Examples, while useful, may be perceived as being proscriptive.	Recommend dropping these examples as the will appear proscriptive on the agency's part. Each company ought to be allowed to define "critical" based on its read of the document. These examples could be placed in an attachment of on an accessible web site.
538	All of the operating parameters . . .	"All of" is redundant in this context.	Delete "All of"
555, 586, 1637	Potency	Potency is not a part of the CMC submission.	Delete "potency."
555-618	Definitions and intent of Reprocessing and Reworking	The definitions and intend are different from those discussed in Q7A.	The Q7A guidance is globally accepted as a GMP standard and we would strongly urge the agency to ensure that the definitions and expectations in this guidance around these two topics is in agreement with Q7A.
555	Reprocessing and adverse effects	"Adverse effects" is confusing. What is important is that the material still meets specifications.	Suggest rewording "Moreover, reprocessing and reworking operations should be capable of producing an improvement in one or more quality attributes without cause other quality attributes to fail specifications."
558-563	Rework operations	This guidance suggests that reprocessing procedures need not be filed, so the operations described should be designated as rework not reprocessing.	Insert the word "rework" in front of operations (line 558) and in front of operation (line 560).
569	Recrystallization as a reprocessing procedure.	This call special attention to repeating a crystallization that is not warranted. Repeating any step is part of the acceptable definition of reprocessing.	Change "repeating a crystallization or other appropriate chemical" to "repeating an appropriate chemical." Then add "crystallization" to the terms in the parentheses. There is no need to call special attention to this process relative to the other examples provided.



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

602	Reworking	A company needs to be able to determine the reason for a rework and this may be legitimately beyond the definition in this draft guidance.	Delete the words " <u>that does not conform to a standard or specification</u> ". This presumes that the only reason one would want to rework would be for this reason. A company may have another legitimate reason and should be allowed to rework as long as the other requirements are met.
626	Impurity levels.	Impurity levels aren't necessarily the only thing to worry about with solvent and/or reagent recovery. You need to control it, you need to meet the appropriate specification (for the intended use) to allow the material to be used again. That's the principle that needs to be met.	Drop the words "so impurity levels do not increase over time."
628-637	Recovery solvents	This is a super section	No action necessary.
681-695	Definition of Starting Materials	Q7A was written such that GMPs anticipate the filing definition. They need to be the same for the sanity of both the agency and the industry.	Delete this definition and reword such that it is consistent with Q7A. An open meeting with the agency to reach agreement would be welcomed.
713	Flow diagram for starting material	This goes beyond what is reasonable. Providing a flow diagram for starting materials doesn't really make much sense. This is the starting point. Specifications should suffice.	Delete bullet
769-77	Critical Process Steps and Operating Parameters	This is a new requirement and this first paragraph needs to be focused. The concept of postsynthesis materials can be eliminated as well.	Replace the entire paragraph with the following: "In this section of the application, the critical operating parameters, process tests and tests performed on intermediates, and final drug substance should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified."



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

807-810	Acceptance criteria for intermediates relative to final drug substance	This requirement may be over restrictive. Example: An acceptable level of residual solvent may be higher in an intermediate than in the final product, so the residual solvent acceptance criteria for the in process measurement on the intermediate would be higher than those in the final product. This is actually often the case where the process removes the solvent prior to the drug substance anyway.	Reword: When the same analytical procedure is used for both the in-process test and the drug substance test, the acceptance criterion for the in-process test should be demonstrated to be <u>appropriate such that the drug substance will meet its acceptance criterion.</u>
839-864	Postsynthesis material and unfinished drug substance	Postsynthesis material and unfinished drug substance are unnecessary new terms. Adds complexity and confusion around a material that is already adequately defined in the document.	Delete these sections.
883	Submission of reprocessing validation information	This guidance already states that reprocessing does not require prior submission so what is validation necessary.	Remove reference to reprocessing.
984-85	Screening solvents	This suggestion is not necessary and could actually lead to work that would otherwise not be necessary.	Eliminate entire sentence beginning "However, screening a variety . . ."
1009	Potential impurities	Being required to identify "potential impurities" seems excessive. We need to focus on impurities actually seen during development and not be required to guess about impurities that have never been seen.	Remove the words "and potential"
1019	Potential impurities		Delete bullet (see 1009)
1037-47	Attempts to identify all impurities	The requirements for impurity characterization have been adequately detailed. This paragraph is redundant will cause a lot of unjustified work.	Delete paragraph.
Table 1	Unspecified Impurities: Any Unspecified	Level in the table is inaccurate and not in agreement with ICH.	Change to 0.10%
1165-78	PQIT	This really a GMP issue since it is part of specs, and not a filing issue.	Delete entire section.
1196	Reference to other draft guidances	These guidances are not finalized.	Delete all references to other draft guidances. All right to reference finalized guidances.



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

1558	Reference to forthcoming Drug Product Guidance	Not needed.	Delete
1667	Attachment 1	The whole section is troublesome from a science and risk perspective. Furthermore, it is not consistent with Q7A.	P&GP would welcome the opportunity to dialog the topic of filing starting material definition in much the same manner as BACPAC was handled. (See General Comments as well)
1683	A drug substance as a starting material for another DS	This seems overly restrictive. What about a drug isolated from nature that is then the starting material for another drug?	Recommend deleting the sentence starting with "A drug substance that is used to synthesize another drug substance. . ."
1696-1719	Significant Nonpharmaceutical market	This represents too high a degree of regulation per FDA's science-based approach and the industry's scientific ability to measure the quality attributes of chemical materials. Good science at the chemical process R&D coupled with the development of appropriate specifications should be the PRIMARY criterion by which a RSM can be chosen.	Delete entire paragraph beginning with "A significant nonpharmaceutical market . . ."
1698	More perspective on significant nonpharmaceutical market.	Whether a starting material has a significant "non-pharmaceutical" market has little or no bearing on the quality of the material. It is irrelevant whether a starting material is made mostly for non-pharmaceutical use or pharmaceutical use. Determination of whether a material should be a starting material should focus on the technical and scientific justification (appropriate specifications, possible impact on the quality of the drug substance, etc.) rather than this extremely subjective measure of "non-pharmaceutical" market.	This "non-pharmaceutical" criteria does not add risk or science based value to the guidance and we recommend that it be removed.



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

1725-28	Selection principles for starting materials	Again the reference to nonpharmaceutical market doesn't have a place in the Agencies current GMP science-based approach.	Replace entire two sentences with the following: "Each proposed starting material is chosen at a point in the process to ensure the following:"
1740	Propinquity	This whole section could and should be eliminated as part of a science-based rewrite of the entire starting material attachment. If sufficient technical or scientific evidence exists to show that a material a single step from the final intermediate can be adequately controlled by specifications and the process itself, there should be no reason not to designate it a starting material. This requirement is again, very vague and subjective. A more objective approach should be taken (appropriate specifications, demonstration that the filed process is not sensitive to the starting material quality, etc.)	Delete the entire section.
1756	Salt Interconversion	Overly restrictive especially if a salt interconversion involves a significant purification procedure.	If propinquity stays in then suggest that the inter-conversion of salt to and from its free acid or base be considered a reaction step provided that step is accompanied by a purification step. The accompanying purification reduces the risk of starting material impurities being carried through into the final drug substance.
1778	Impurities in the starting material	This statement is confusing since the impurities in the final drug substance are qualified and specified.	Amend this to state that impurity levels in the starting materials must be specified and ensure the quality of the drug substance.
1785	Significant level of impurities in Starting Materials	This is too arbitrary. Again, if the impurity has been appropriately qualified and is controlled, there should be no issues with using starting materials that have impurities greater than 0.10%, especially since the quality of the drug substance is controlled.	Remove this requirement.



P&GP Comments on FDA Draft Guidance for Drug Substance CMC Information

1815-1818	Advanced techniques	Again, we need to rely on good science in making an appropriate determination of designated starting material.	Suggest rephrasing. "So long as a proposed starting material can be distinguished from potential isomers and analogs using commonly available techniques (including NMR, MS, EA, X-ray, chiral HPLC, etc.), it may be an appropriate starting material.
1833-1836	Flow diagram	Providing information prior to the designated starting material is not scientifically justifiable and adds a lot of work and unnecessary information gathering to the filing process for both the Agency and industry.	Strongly urge that this be rewritten. Simply ensuring that the starting materials are well qualified and specified and provide the Agency with a comfort level to be able to evaluate the safety and quality of the drug substance should suffice.
1860	0.10% impurity requirement	Again, if the impurity is adequately qualified in the drug substance and controlled in the starting material, levels above 0.10% should not be an issue.	Delete this requirement for 0.10%.
1875	Significant nonpharmaceutical market	Starting materials should be held to the same technical/scientific justification whether they are from significant "non-pharmaceutical" markets or not.	Remove special requirement for nonpharmaceutical market.
1884	Examples of manufacturers	This requirement is archaic and not science-based. Will not ensure quality anyway.	Delete bullet.
1886	"Confirmation that (1) the drug substance manufacturer did not . . ."	how does this ensure the quality of the final drug substance??	Delete bullet.
1919	Carryover of Impurities.	This is not science-based based on arguments already made for inappropriate impurity requirements for starting material definition.	Delete section c.
2184-94	Postsynthesis materials	Again, this special designation is viewed as additional information that is really not useful and adds to the regulatory burden.	We recommend that this be removed.
2199	Postsynthesis materials tests.	If postsynthesis materials go then the tests are not needed.	Delete this definition.