



June 28, 2004

Via fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-00571

Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing, and Controls Information [Federal Register Volume 69, No. 4, page 929-930, January 7, 2004]

Dear Sir/Madam:

Aventis appreciates the opportunity to comment on the above-referenced Draft Guidance for Industry entitled "*Drug Substance; Chemistry, Manufacturing, and Controls Information*".

The Agency states that the draft guidance provides recommendations on the chemistry, manufacturing, and controls (CMC) information for drug substances that should be submitted to support original new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), and abbreviated new animal applications (ANADAs). The draft guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format.

We offer the following comments and questions for your consideration.

GENERAL COMMENTS:

While we welcome the concept of the guidance and see many well-designed details, in our opinion the general concepts of the science-based and the risk-based approach need to be taken further into the spirit and details of the guidance text. This is particularly important for Attachment 1, which we suggest should be redesigned.

The decisive criterion for the selection of a starting material is the fact that changes in its manufacturing process is unlikely to affect the safety and quality of the finished drug substance. As long as this can be demonstrated and justified applying acceptable risk-based criteria and sound science, all other criteria are secondary.

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Specifically, we fail to understand why the fact that a commodity chemical is available on the non-pharmaceutical market improves its quality assurance. In our experience, the contrary is possible.

SPECIFIC COMMENTS:

Lines 56-68: *“This guidance does not provide specific recommendations relating to the following:*

- *Monoclonal antibodies*
- *Peptides*
- *Oligonucleotides*
- *Radiopharmaceuticals*
- *Medical gasses*
- *Drug substances that are not well characterized (e.g., botanicals, some proteins) derived from plants or animals*
- *Drug substances derived using transgenic technology*
- *Drug substances derived directly from or manufacturing operations involving fermentation (conventional fermentation or using rDNA technology) or tissue or cell culture.”*

Recommendation: For clarity, we suggest revising “*Peptides*” to “*Synthetic Peptides*” or adding “*Synthetic Peptides*” as “peptides” can be interpreted as “synthetic peptides” or possibly “proteins”. We also suggest including “*Synthetic Oligonucleotides*” as synthetic peptides and synthetic oligonucleotides are produced by standard chemical reaction steps and the materials employed are well-characterized standard materials. Thus, no biological system is involved for the generation of these molecules. Accordingly, they should be treated as chemicals.

Lines 76-79: *“FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.”*

Recommendation: We suggest adding the following sentence as there should be a reference to the FDA policy and the opportunity to allow application of RBA principles: *“In particular, application of risk assessment principles, which are in line with FDA’s Risk Based Approach, can justify a different approach.”*

Lines 107-109: *“In some cases, the majority of information to address the drug substance sections will be incorporated by reference from a master file (see section II.D.2).”*

Recommendation: We suggest adding “(see section II.D.2)” following “subsections” to alert the reader where information provided by the applicant is defined. Referencing specific sections in the guidance will provide added clarity.

Lines 203-290: *Entire Master Files (MFs) section*

Recommendation: It is not clear where information should be included: Master File and/or applicant information. For clarity, we suggest a more common understanding of the Master File (as in the EU), with a division into open and closed parts.

Regarding sterile API, is the sterilization of active substance part of the Master File or applicant information?

Regarding Container Closure System (Lines 268-270), for clarity, we suggest adding an example of the specific type of information to be included in the application.

In addition, since the Appendices (Lines 277-278) refer to information on facilities/equipment and information, for clarity, we suggest adding an example of the specific type of information to be included in the application beyond what is provided in the Master File.

Lines 293-368: *Entire Section III. General Information*

Recommendation: For clarity, we suggest that Section III should be headed “Content of a CTD-format CMC (Drug Substance)” and the following sections (from III.A to IC.C) should be numbered and headed according to the sections of the CTD-Q Module 3.2.S.

Since some information may not be required for marketed drug substances (e.g., used for generics), for clarity, we suggest that this be clearly indicated.

Lines 379-381: “*Each site should be identified by the street address, city, state, and when available, the drug establishment registration number.*”

Recommendation: Is the establishment registration number to be provided for foreign establishments? Or, are details on the US agent considered to be sufficient?

Lines 386-388: “*Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug establishment, as required under 21 CFR 207.40(c), should be included.*”

Recommendation: Since the agent name is subject to change, is this necessary? We recommend replacing the name of the agent with the title of the agent to avoid updating the application with personnel changes.

Lines 406-436: *Entire “Flow Diagram” section*

Recommendation: We suggest that flow diagram should not include so many details. Process controls, operating parameters, expected yields are thoroughly described in the narrative and should not be repeated here.

The flow diagram should state only critical operating parameters (Line 427) particularly for this section on the Flow Diagram. We recommend that process parameters be part of the narrative description rather than the flow diagram, or that an example is given of a more critical process parameter that would be useful on the flow diagram.

Since expected yield (Line 431) is part of the narrative description for the process, we suggest that it should be eliminated from the flow diagram. to reduce redundancy of information.

“Critical process controls” should replace *“All process controls”* (Line 426).

Lines 442-444: *“The description should identify all process controls and the associated numeric ranges, limits, or acceptance criteria.”*

Recommendation: We suggest that *“all process controls”* should be replaced by *“critical process controls”* and that *“critical”* should be described as *“critical for the quality of the drug substance”*. To list and/or to describe all process controls increases regulatory burden, and seems unnecessary. The process controls listed/described in the dossier should be those which have been demonstrated to be essential to monitor and adjust the process, in order to guarantee the quality for the final drug substance.

Line 449: *“ • A detailed description of each manufacturing step”*

Recommendation: For clarity, we suggest that a cross reference be made here to Lines 1753-1757 be made here for the definition of *“step”*.

Line 454: *“ • Type of equipment (e.g., Centrifuge) used, including materials of construction when critical”*

Recommendation: We suggest adding text that provides clarification on the type of equipment that should be used.

Lines: 459: *“ • Type of analytical procedure (e.g., HPLC) used for each process test”*

Recommendation: Does this also require a description of the analytical method (i.e., type of column, wavelength, eluent etc.)? We suggest adding text to clarify.

Lines 466-467: *“ • Identification of manufacturing steps that use recovered solvents or auxiliary materials (see section IV.B.3.c)”*

Recommendation: We suggest deleting this bullet point as it is not necessary as part of the filing.

Lines 475-484: *“Moreover for drug substance derived from a biological source or a semisynthetic drug substance, the description should include information on the*

processing operations conducted on the biological starting material and other procedures such as:

- *Storage and transportation conditions for biological starting materials*
- *Preparation procedures (e.g., cleaning, drying)*
- *Isolation processes (e.g., grinding, cell lysis, extraction from biomass)*
- *Holding times and storage conditions during manufacture*
- *Procedures used to maintain traceability of all intermediate and drug substance batches back to the batches of the starting material”*

Recommendation: For clarity, we recommend that a reference be made to Section IV.C.1 (Starting Materials) where this concept of “*biological starting material*” and “*API starting material*” is introduced. Also, in the last bullet point, the guidance refers to “*batches of the starting material*”, is this reference to the “*biological starting material*”? We suggest adding text to clarify.

Lines 488-491: “*A statement should be provided that bovine-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility.*”

Recommendation: We suggest revising this sentence to read as follows: “*A risk assessment to prevent BSE contamination should be provided.*” As the BSE risk is determined by the material, the process and the risk of cross contamination conducting a specific risk assessment in any case of animal origin material would insure low BSE risk. Further, since areas of BSE/TSE risk are increasing, focusing on BSE countries only would not be sufficient. We also suggest adding information on supplier qualification for Adventitious Agents (BSE/TSE/Viral Safety).

Lines 510-511: “ • *Environmental controls – conditions associated with the manufacturing facility (e.g., temperature, humidity, cleanroom classification).*”

Recommendation: We suggest deleting this bullet point, as the environmental control is only important if the material is handled in an open area, there fore it is not necessary to submit all room classifications.

Lines 521-522: “*All process controls, critical or otherwise, should be included in the description of the manufacturing process*”

Recommendation: We suggest adding text to clarify the expectations for non-critical process controls (i.e. does this include monitoring tests or tests “for information only”?).

Lines 541-543: “ *All tests on intermediates, postsynthesis materials, and unfinished drug substance should be listed in the description of the manufacturing process in S.2.2 and described in S.2.4.*”

Recommendation: For clarity, we suggest revising this sentence to read as follows: *“Tests on intermediates required to ensure the quality of the final drug substance should be listed in the description of the manufacturing process in S.2.2 and described in S.2.4.”*

Lines 576-579: *“Repetition of a single reaction step should be carefully evaluated with respect to the potential formation of by-products and over-reacted materials. Repetition of multiple reaction steps is considered to be reworking, rather than reprocessing.”*

Recommendation: We suggest adding text to include information from ICH Q7A 14.22 on introducing unreacted material back into the process. We also suggest that *“reworking”* and *“reprocessing”* be defined as in ICH Q7A.

Lines 587-589: *“ For example, CDER would consider reprocessing proteins to be reprocessing operations that should be described in the application.”*

Recommendation: For clarity, we suggest revising this sentence to read as follows: *“CDER would consider reprocessing proteins, as covered in this guidance, to be reprocessing operations that should be described in the application.”*

Line 620: *“c. Recovery”*

Recommendation: Since Recovery is a GMP activity, we recommend that it should not be part of the synthesis description. In the case of a non-standard process, the description can be required here.

Lines 639-643: *“ Recycling of filtrates should be included in the description of the manufacturing process if these operations are performed. Information should be provided on the maximum number of times material will be recycled and for the process controls for such operations. Data on impurity levels should be provided to justify recycling of filtrates.”*

Recommendation: For clarity, we suggest that the number of times filtrates are recycled should only be provided when critical.

Line 645: *“ d. Regeneration”*

Recommendation: Since Regeneration should be regarded as standard GMP handling, we recommend that it should only be included for a non-standard process.

Lines 657-662: *“ The recommendations for reworking apply to (1) recovery of a drug substance from drug product or drug product in-process materials or (2) a drug substance, after it has been released by the quality control department, that undergoes processing to bring the material back into conformance with its specification (e.g., purification of aged material to decrease the level of degradation products to conform with the approved acceptance criteria).”*

Recommendation: We consider repurification of aged material by reprocessing to be of no additional risk, with appropriate validation addressed. There is no reason to treat this different from other reprocessing. Therefore, we recommend deleting these lines.

Lines 688-689: “ *In general, the starting material and API starting material should be the same for a synthetic drug substance.*”

Recommendation: We suggest that this statement should be revised to read as follows: “*For synthetic drug substances, the starting material and the API starting material are the same.*”

Lines 689-691: “ *However for a drug substance to be derived from a biological source, the starting material (e.g., plant) and AOI starting material (e.g., extract) can be different.*”

Recommendation: Can the compound extracted from a natural source be a “*starting material*” for a semi-synthetic drug substance? If so, for clarification, please indicate where information on the control of this starting material is discussed in the guidance. Lines 689-691 refer to an “*API starting material*” as an “*(extract)*”, while Lines 2001 and 2079 refer to an extract as an “*intermediate*”.

Lines 697-698: “ *Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance.*”

Recommendation: For clarity, we suggest adding the following text: “*Drug substances are described in official compendia.*”

Lines 713: “ • *A flow diagram*”

Recommendation: We suggest that text be added to provide clarity on what should be included in the flow diagram. It is unclear whether this applies to the starting material or the drug substance.

Lines 723-725: “ *The following information should be submitted in S.2.3 for reagents, solvents, and other auxiliary materials (e.g., filter aids, decolorization agents) used in the manufacture of a drug substance.*”

Recommendation: Is it sufficient to indicate the general type of filter aid used? We suggest adding text to clarify.

Lines 785-788: “ *Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in S.4.4) should be provided as part of the justification. Additional information should be provided in this section (S.2.4) under the following circumstances.*”

Recommendation: We suggest that this information should only be requested for a new drug substance.

Lines 810-812: “ *Tests performed in-process in lieu of testing the drug substance should be included in the drug substance specification (S.4.1) and the results of such tests should be included in the batch analysis report (e.g., certificate of analysis).*”

Recommendation: We suggest adding text to clarify the reference to Certificate of Analysis as these are not necessarily in CTD Section S.4.4 Batch Analyses. CTD Section S4.4 can be tabulated data for organizational purposes.

Lines 839-854 and Lines 856-864: Entire section for “• *Postsynthesis Materials*” and entire section for “• *Unfinished drug substance*”

Recommendation: We suggest combining sections for “*Postsynthesis Materials*” and “*Unfinished DS*” into one category called “*Pre-Drug Substance Materials*” to simplify the process and to be harmonized with ICH Q7A. The need to have a differentiation between “*Postsynthesis Materials*” and “*Unfinished DS*” is unclear. The same information seems to be required for all of these materials, therefore one category should be necessary.

Lines 900-903: “*If in vitro studies (e.g., dissolution) or in vivo studies (e.g., bioequivalence) on the drug product were warranted because of a change in the drug substance manufacturing process, the study results should be summarized, and a cross-reference to the studies (with study numbers) should be provided in S.2.6.*”

Recommendation: For clarity, we suggest that these studies should be cross-referenced with pharmaceutical development in Section P.

Lines 931-933: “*Issues such as counterion stoichiometry, regiochemistry, geometric and configurational isomerism, and absolute stereochemistry should be addressed.*”

Recommendation: We suggest adding text to clarify the requirements for “*counterion stoichiometry*” and “*regiochemistry*”.

Lines 1059-1060: “• *Summary of the route of synthesis or method of preparation if the impurity or potential impurity was independently prepared*”

Recommendation: We suggest eliminating this requirement, as there is no added value of providing the route of synthesis if the impurity is characterized.

Lines 1111-1114: “ *The specification from the applicant and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacturer’s certificate of analysis (COA).*”

Recommendation: We suggest eliminating this sentence, as tests will be accepted from the supplier according to the status of the supplier certification and according to continuous evaluation. This is not a constant process. Since the applicant has to guarantee compliance to the specifications in any case, this provision is unnecessary.

Line 1129: “*Table 1: Specification for Synthesized Drug Substance X*”

Recommendation: The acceptance criteria for appearance “white crystalline powder” may be misleading, as it is not possible for most drug substances to determine “crystallinity” by visual inspection. For clarity, we suggest adding more descriptive text for the acceptance criteria.

The acceptance criteria of “*NMT 0.1%*” for “*Any unspecified*” unspecified impurities is not consistent with ICH Q3A or Lines 1785 and 1922. For consistency, we suggest that the acceptance criteria should be revised to state “*NMT 0.10%*”.

Lines 1205-1208: “ *If the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure are not modified, the analytical procedure need not be provided.*”

Recommendation: For clarity, we suggest adding “(e.g., USP/NF, EP, JP)” after “*official compendium*” to include mention of all acceptable compendia.

Lines 1219-1220: “ *Analytical procedures from any other published source (e.g., another country’s compendium, scientific journal) should be provided.*”

Recommendation: In the case of global submissions, would references to major regional compendia (i.e., EP, JP, BP) not be accepted without providing a copy of the procedure? At least all compendia of the ICH regions should be accepted. The requirement to provide the analytical procedure from another country’s compendium (e.g., EP or JP) is not consistent with the principle contained in Footnote 21, in which it is stated that citation of a compendium means the current revision of the cited compendial monograph is used. The requirement to provide the analytical procedure from another country’s compendium would mean that the version of the analytical procedure (from e.g., EP) submitted in the NDA would become outdated as soon as the next revision of the EP is effective. We suggest that for any analytical procedures cited from widely

available national compendia (e.g., EP, JP, BP, etc), it not be necessary to provide the text of the monograph or analytical procedure.

Lines 1263-1265: *“The batch analysis reports should include results from all tests performed on the batch, including tests that are not part of the proposed specification. References to analytical procedures should be provided.”*

Recommendation: We suggest deleting “...tests that are not part of the proposed specifications” or adding text to for clarification. Are they tests applied during development studies and not eventually retained for specification? If so, we suggest that text be added to clearly indicate that these tests are to be included only for development batches. If not, we suggest deleting “...including tests that are not part of the proposed specification” as during process development many tests are applied just to investigate the process and are not relevant for the quality of the drug substance in all cases, especially in early stages of the development.

Lines 1340-1341: *“Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability.”*

Recommendation: For clarity, we suggest adding text to define “reasonable allowance”. If the highest level of a particular impurity was observed at 0.4% and qualified, is NMT 0.5% (25% higher) specification acceptable to the Agency?

Lines 1411-1414: *“The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided.”*

Recommendation: For clarity, we suggest adding text to provide an example of “functional secondary packaging components”. We also suggest deleting “For nonfunctional secondary packaging components...”.

Lines 1430-1434: *“The discussion should include for example (1) a summary of the stability batches tested, storage conditions used, attributes tested, shelf-life acceptance criteria,”*

Recommendation: For clarity, we suggest adding text to define the term “shelf-life acceptance criteria”. Is there a possibility that there can be different acceptance criteria for the release of the Drug Substance?

Lines 1717-1719: *“See sections I and II of this attachment, respectively, for selection principles and recommendations on the documentation that should be provided for these starting materials.”*

Recommendation: In addition to this sentence, we suggest adding the following text: *“In case sound scientific judgment and appropriate risk assessment demonstrate the proposed starting material is well characterized, has a well-defined and controlled impurity profile, and changes in its manufacturing process are unlikely to affect the safety and quality of the finished drug substance, the selection principles in section I of this attachment need not apply.”*

Lines 1784-1786: *“For purposes of selecting proposed starting materials, a significant level is considered to be greater than 0.10 percent in the drug substance (0.20 percent for veterinary drug substances not used in human drug products) of any of the following impurities:”*

Recommendation: The threshold of 0.1% in the starting material is too tight. For clarity, we suggest adding text to provide the rationale for why a starting material should not be the source of significant levels of impurities in the drug substance (i.e., significant being greater than 0.1% in the drug substance). See also Lines 1859-1863. We suggest that this section should be consistent with ICH Q3A(R).

Lines 1792-1797: *“Moreover, a proposed starting material should be at or before the point in the manufacturing process where transmissible spongiform encephalopathy (TSE) agents can be introduced into the process. For example, if a chemical is produced using an enzyme that can introduce TSE agents into the process, the proposed starting material should be prior to the enzymatic step regardless of whether the chemical is consistent with all other selection principles.”*

Recommendation: Since all steps in the synthesis of the starting material and the drug substance are to be BSE/TSE free, is this statement necessary? Further, if a sponsor gets agreement from the Agency regarding the designation of a starting material and then later finds a BSE/TSE risk in the manufacture of the starting material, would this require a new designation of starting materials? Statements from the drug substance manufacturer, and from the starting material manufacturer, and from the starting material manufacturer when appropriate, should be considered adequate to warrant that there is no BSE/TSE risk.

Lines 1811-1814: *“However, data demonstrating that instrumental techniques commonly used for identification tests (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy) are specific can be provided to justify proposed starting materials that the Agency might otherwise consider to be too complex.”*

Recommendation: Since HPLC is a routine method, we suggest that “normal phase and reversed phase HPLC” are included in the examples of instrumental techniques used for identification tests.

Lines 1815-1818: *“If advanced techniques suitable for complex structures (¹H-NMR, ¹³C-NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral*

HPLC) are needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not an appropriate candidate for designation as a starting material.”

Recommendation: What is the scientific rationale for not accepting advanced techniques? We suggest that the judgment should be science-based.

Lines 1831-1841: Entire section “ *B. Flow Diagram of the Complete Synthesis*”

Recommendation: We suggest that it is not necessary to provide a complete flow diagram in Section S.2.3, as the flow diagram in Section S.2.2. should be cross-referenced.

Is it a new requirement that flow diagrams should start with compounds with a significant nonpharmaceutical market even when they are not starting materials? We suggest that the statement on Lines 1834-1836 (“*Each synthesis branch should begin with chemicals that have a significant nonpharmaceutical market, regardless of whether these chemicals are being proposed as starting materials.*”) is contradictory to Lines 1676-1677 (“*The description of the manufacturing process in an application begins with the starting material or materials*”)

Lines 1859-1863: “*Moreover, FDA recommends that acceptance criteria be established for all organic impurities that occur above 0.10 percent and that a limit of NMT 0.10 percent be established for unspecified organic impurities when there is greater potential for impurities originating from the starting material to carryover to the drug substance (0.20 percent for a veterinary drug substance not used in human drug products).*”

Recommendation: We suggest that no fixed limits such as 0.10% for organic impurities should be required for starting materials. The limits must be defined by a scientific rational and appropriate risk assessment regarding the process, in order to guarantee compliance to the specified impurity limits of the final drug substance.

The example drug substance specification table (Table 1 - Line 1129) lists organic impurity limits with one significant figure. However, Lines 1859-1863 mentions limits of NMT 0.10% (two significant figures). For clarity and consistency, we suggest making a revision to either Table 1 or to the text within Lines 1859-1863.

Lines 1909-1911: “*The flow diagram provided in S.2.3 will indicate the separation between the final intermediate and the proposed starting material. A cross-reference to the flow diagram in S.2.3 is sufficient.*”

Recommendation: This statement suggests that a flow diagram should be included in Section S.2.3 Control Materials, but also suggests a cross reference to the same section (Section S.2.3). We suggest adding or revising text for clarification.

Lines 1915-1917: *“The starting material specification and the flow diagrams provided in S.2.3 should indicate whether a proposed starting material is an isolated and purified substance. Therefore, cross-reference to this information is sufficient.”*

Recommendation: Lines 1770-1773 have already discussed that the starting material should be an isolated and purified substance.

Lines 1919-1924: *“c. Carryover of Impurities
Impurities reported in S.3.2 that are found in the drug substance at levels greater than 0.10 percent (0.20 percent for a veterinary drug substance not used in human drug products) should be listed in S.2.3, or a cross-reference should be provided to the information in S.3.2.”*

Recommendation: This discussion is part of S.3.2. We suggest that the rationale should be provided for restricting the origin of impurities in the drug substance to other sources than the starting material.

Impurities in the drug substance of greater than 0.1% are discussed under Section 3.2.S.3.2 Impurities. Impurities listed in Section 3.2.S.2.3. Control of Materials would only be starting material impurities. We suggest that any impurities in the starting material of greater than 0.1% that are not reduced through the synthesis process make the starting material unacceptable.

Why can an impurity not come from the starting material, if the qualification of the impurity is performed by toxicological tests?

Lines 1984-1988: *“It is valuable for drug substance manufacturers to maintain close communication with manufacturers of starting materials. The quality of a starting material can be affected by changes in manufacturing process (e.g., changes in solvents, purification, catalysts, route of synthesis), and knowledge that a change has taken place can assist a drug substance manufacturer in maintaining a valid starting material specification.”*

Recommendation: We suggest that a written commitment from the starting material supplier (to set suitable specification in accordance with the manufacturing process, and to inform the drug substance manufacturer about any significant changes) could be an acceptable alternative to providing full data on the starting material.

Lines 1998-2001: *“The term drug substance derived from a biological source includes drug substances that are the chemical obtained directly from the biological source and semisynthetic drug substances that are produced by modification of a chemical (i.e., intermediate) obtained from the biological source.”*

Recommendation: The extract is referred to as an intermediate in lines 2001 and 2078-2079. However, in lines 690-691, the extract is referred to as the API starting material. We suggest adding text or revising text for clarification and consistency.

Lines 2024-2027: *“Applicants should provide the following information in S.2.3 for plant or animal starting materials. For semisynthetic drug substances the information recommended in Attachment 1 should be provided for the starting materials of synthetic origin, if there are any, in addition to the information provided for the plant or animal starting materials.”*

Recommendation: For clarity, we suggest revising the text to read as follows: *“Applicants should provide the following information in S.2.3 for plant or animal starting materials that do not have significant nonpharmaceutical market before they were used in the drug substance synthesis.”* We suggest that this reinforces information provided in Lines 2016-2018.

Line 2071: *“... drug substance (see sections V.A, V.D, and V.E of this guidance).”*

Recommendation: For accuracy, we suggest revising the text to read as follows: *“... drug substance (see sections VI.A, VI.D, and VI.E of this guidance).”*

Line 2107: *“Glossary”*

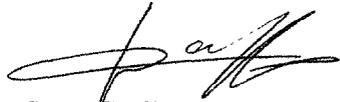
Recommendation: We suggest that the terms *“Sunset testing”* and *“PQIT”* should be added to the Glossary.

Lines 2137-2139: *“The term drug substance can also be used to refer to a physical mixture of two or more drug substances used to produce a fixed-combination drug product.”*

Recommendation: Is the term *“drug substance”* identical with the term *“Active Pharmaceutical Ingredient”* as used in ICH Q7A?

On behalf of Aventis, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing, and Controls Information* and are much obliged for your consideration.

Sincerely,



Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs