

July 6, 2004



Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

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Re: Docket Number 2003D-0571
Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing, and Controls Information

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including general and specific comments for the Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing, and Controls Information. These comments are presented for consideration by the FDA. The general comments are presented first, with the specific comments presented in order by section and line number in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Mary Faye S. Whisler".

Mary Faye S. Whisler, Ph.D.
Assistant Director
Global New Submissions, North America

2003D-0571

C22

Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing, and Controls Information

GENERAL COMMENTS

It is understood that FDA is currently working to prepare a specific guidance proposing a 'risk based' approach to assessment of TSE risk for medicinal products. It would therefore seem appropriate to avoid defining any prescriptive requirements as regards TSE risk assessment criteria or supporting documentation requirements in this guidance. Other forthcoming guidances are mentioned in the guidance. Both FDA and industry would benefit from the issuance and finalization of these guidances.

The definition of critical steps in the manufacturing process is excessive and should not be a requirement. Specific operations within the steps may need to be conducted under very precise operating conditions and such operating parameters may be described as critical. The regulatory status of non-critical controls should be clarified, both in respect to compliance with cGMP and also with respect to regulatory activity required, if such controls are changed. It should be stated that non-critical controls are not mandatory and not a compliance issue.

The inclusion of both synthetic and some types of biological drug substances within the scope of the guidance makes interpretation of certain aspects of the guideline difficult. "Derived from a biological source" and "biological starting material" are not helpful terms in connection with manufacture of drug substances. All organic compounds are ultimately derived from biological sources. It may be reasonable to regard the biological source as the starting material where the drug substance is derived using physical separation processes with no chemical modification. But it is not reasonable to regard any such sources as starting materials when they are extracted or similarly physically processed to yield highly purified and well-characterized substances used to manufacture semisynthetic or totally synthetic drug substances. For those sections of the guideline addressing requirements for adventitious agents safety evaluation, it is unclear in places which aspects of the requirements are targeted at biologics, and which (if any) are also applicable to products of chemical synthesis.

Starting materials are also an issue as relates to the definition that they should have "significant non-pharmaceutical market". This should be deleted from the guidance. It is the quality of the starting material (and not its origin or its other uses) which determines suitability as an input to manufacture of drug substance. Materials with no "non-pharmaceutical market" are likely to be of higher quality and manufactured in superior facilities. They are therefore more suitable, not less suitable, as starting materials.

Additionally, propinquity is not adequately defined. "Propinquity" should be measured by the number of purified intermediates between starting material and drug substance. Each purification, by definition, effects a reduction of impurity levels and an increase in quality. Isolation of the intermediate, for example, by crystallization, is one method of purification, but effectiveness may be limited by a requirement to heat the crystallizing solution and to dry the crystalline product. Each of these can lead to degradation. Therefore intermediates demonstrably purified in solution (i.e., by an extractive work-up) should be counted when determining propinquity. Also conversion of a salt to its free acid or base form (or vice versa) can effect purification and should also be counted when determining propinquity. "Post synthesis materials" is not a helpful descriptor for such intermediates.

Many compounds produced by biosynthesis have complex molecular structures and multiple chiral centers. Steroids are but one example. Although such compounds have multiple potential isomers, in practice most of these isomers may be inaccessible and the risk of mistaken identity is negligible. Proposals for compounds with complex molecular structures as starting materials should be acceptable provided that the compound can be distinguished from isomers and analogs, which are realistic substitutes or impurities. Applicants should be free to use any analytical method to demonstrate distinct identity.

Overall this draft represents an escalation of requirements from the previous drug substance guidance. The guidance uses a low or no-risk approach. The document should allow for application of risk-based approach for inclusion of information. It requires excessive control of the manufacturing process (too many stages in too much depth) and excessive analytical controls on too many precursors of the drug substance. Additionally, the application of the regulatory relief initiative should be incorporated into the document.

Specific Comments

Lines 49 – 51: Clarity is needed to define the terms in these bullets. These terms are the basis of this guidance and need definition. Change the term "intermediate" to "chemical substance" in the third bullet. Add "without chemical modification" to the end of the phrase in line 49. Add footnote 4 to line 50.

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Line 472: Clarity is needed on the inclusion of yield ranges.

Lines 474 - 483: "Derived from a biological source" and "biological starting material" are not meaningful terms. All organic compounds are ultimately derived from biological sources. Use suggested text for line 49. It is not justified to require this type of information for a semi-synthetic drug substance which results from chemical modification of a highly purified and well-characterized substance derived from plants or animals. Delete lines 478-483 unless well clarified.

Lines 488-491 and lines 1525-1527: The country of origin of a particular material of bovine origin is not the sole determinant of the risk of TSE transmission posed by that material. Other factors, such as tissue used, age of animal, processing, route of admin and dose are all thought to influence the potential risk. The fact that a material is bovine derived and originates from a BSE country as defined by USDA, does not necessarily mean that the material poses a risk of transmission. As written, the guideline would appear to prohibit the use of materials such as milk derivatives within manufacturing facilities if obtained from countries on the USDA list. However, milk derivatives are widely recognized as being safe, regardless of the country of origin. Similar arguments apply to other commonly used materials such as tallow derivatives, amino acids etc. that are considered to pose negligible risk of transmission due to the source tissues used, aggressive processing applied, or both. As noted under General Comments above, it is recommended that guidance on TSE risk minimization be removed from this guideline on the understanding that separate guidance is in preparation by FDA.

Lines 491-493 and 1510-1523: As stated under general comments above, the guideline would benefit from a clearer delineation between the requirements for products of chemical synthesis and those obtained from biological sources so far as guidance on adventitious agents safety is concerned. In particular, certain references are made in the document to the need to consider the risk of cross-contamination, and it is suggested that additional facilities information can be warranted under certain circumstances. It is understood that this is intended to only apply to biologics, but this is not entirely clear in places. To the extent that such requirements might be applied to products of chemical synthesis manufactured using highly processed reagents of animal origin, it is contended that the risk is negligible, and is appropriately handled through application of cGMP. As such, detailed facilities information, or information regarding other materials processed in the same facility, should not be required for such drug substances.

Line 500: Process Controls should be Header 3., not a bullet item.

Lines 514 – 516: Clarify or change the terminology of the two types of process tests. For example, change “in-process material tests” to “control of intermediates”.

Lines 520 – 521: Clarification is needed here. The applicant may choose to apply additional controls that are not registered. Suggested text would be “All process controls, necessary to ensure appropriate quality of the drug substance, should be included in the description of the manufacturing process.”

Lines 540 – 542: Clarification is needed here. Suggested text would be “All tests on intermediates and unfinished drug substance necessary to ensure appropriate quality, should be listed...” and “...in the flow diagram...” should be deleted.

Lines 565 - 618: This section covers reprocessing and reworking. Although the definitions are comprehensive they do not adequately address the issue of intermediate or API salt conversion back to the free base and then back to the same salt and whether it is considered reprocessing or reworking. Suggested text for lines 567-571 is to add neutralization/salt formation in the parenthetical clause so that the sentence reads "Reprocessing is the introduction of an intermediate or drug substance, including one that does not conform to a standard or specification, back into the process and repeating crystallization or other appropriate chemical or physical manipulations (e.g., distillation, filtration, neutralization/salt formation, chromatography, milling) that are part of the approved manufacturing process.

Line 636: Controls of recovered solvents (to a specification) is excessive and should be recovered as fit for purpose.

Lines 666 – 718: All organic compounds are ultimately derived from biological sources. It is not reasonable to regard any such sources as starting materials when they are extracted or similarly physically processed to yield highly purified and well-characterized substances used to manufacture semi-synthetic or totally synthetic drug substances. [It may be reasonable to regard the biological source as the starting material where the drug substance is derived with no chemical modification].

The purified substances used to make semi-synthetic or totally synthetic drug substances should be controlled by specification when used as starting materials. Later compounds in the synthetic sequence may be equally or more suitable as starting materials, particularly if their quality can be better controlled.

Where appropriate the applicant should present a risk assessment concerning control of pathogens, herbicides, pesticides etc. and, if necessary, demonstrate such control in the specifications. Details of the isolation and purification of such substances should not be required for this purpose. This information should be referenced to the appropriate attachment to avoid inconsistencies and duplication. In line 690, add “without chemical modification” after biological source, delete lines 693 – 694 since they duplicate lines 683 – 688, move lines 697 – 701 to line 707 and clarify that these lines also apply to semi-synthetic drug substances, the definition of in lines 701 – 704 should be in alignment with line 49, delete the sentence in lines 703 – 705, and delete lines 710 – 718 as it is defined in the appropriate attachment.

Line 676: Delete "For materials of biological origin,..."

Lines 754 – 761: This section refers to drug product, and should be deleted.

Line 774: Clarify the regulatory status of non-critical controls, both in respect to compliance with cGMP and also with respect to regulatory activity required if such controls are changed.

Lines 796 - 809: In ICH Q3C, it is acceptable to not test for a residual solvent if the levels are below the accepted limits in the materials used. For residual catalysts testing the same should apply, that is, if the level of the catalyst is controlled in one step it does not have to be tested in the subsequent step. It is frequently possible to demonstrate that levels of specific impurities are reduced when an intermediate is processed to drug substance. In such cases the requirement that the acceptance criterion should be identical or tighter in the intermediate is unreasonable. Suggested text is to add, "unless data are provided to justify a lower limit" at the end of sentence.

Line 817: When controls are applied for all reasonable impurities, testing for assay has no added value and should not be required. Delete "assay and" from the sentence.

Line 821: Definition of the substance used at the beginning of a semi-synthetic process, as an intermediate is unreasonable. Change "intermediate" to "substance" or "compound" in the sentence.

Lines 838 – 853: The concept of "postsynthesis materials" is not helpful. Delete this text.

Lines 895 – 896: Clarify the expectation for "Manufacturing changes associated with changes in the impurity profiles of intermediates should also be described".

Line 905: Delete the term "procedures".

Line 917: "Evidence for structure" would be a better term than "Elucidation of structure". Also clarify that not all tests are required for every drug substance and that discretion can be used to choose only the tests necessary to provide adequate evidence of structure.

Line 927: When exact mass is available from mass spectrum of drug substance, elemental analysis adds no value. It should only be required for salts for example.

Line 929: Only single crystal X-ray crystallography (not powder X-ray crystallography) can be used to provide evidence of structure. When single crystal X-ray data are available, no further confirmation of structure should be required. Change text appropriately.

Line 932 – 933: Please clarify meaning of “When the drug substance consists of more than one molecular species”. Does this refer to a drug substance, which is a mixture of close analogues, for example, a polyethyleneglycol ester? If so, the requirement to provide information on each component is unreasonably onerous and could be impossible.

Line 1008: Please clarify “potential impurities”. Confirm that they can be limited to impurities, which might reasonably be expected to be present.

Lines 1056 – 1057: Chemical and particularly physical properties of an impurity or potential impurity should not be required. Delete this bullet.

Line 1087: Delete text “in section” from sentence.

Lines 1087 – 1090: When unfinished drug substance is fully tested and drug substance itself undergoes limited testing, separation of the two specifications to S.2.4 and S.4.1 is not helpful.

Lines 1089 – 1090: Request clarification regarding drug substance specifications for mixtures of two or more drug substances. The draft guidance document implies that specifications must be presented for each individual drug substance, as well as subsequent mixtures of the drug substances. As written, the guidance refers to a specification for a combination of drug substances within the drug product. The wording is unclear.

Lines 1120 – 1122: Clarify the status of alternative analytical procedures, both in terms of compliance with cGMP and also in terms of regulatory requirements to change.

Line 1128 (Table 1): Change text in table in identification test (2) from spectra to spectrum and insert NMT in the acceptance criteria column for heavy metals (NMT 0.0001%). The table gives the impression that inclusion of both Infrared Absorption and HPLC retention time is required to confirm identity. A single specific identification (such as infrared testing) would normally be considered sufficient.

Line 1130 (Table 2): Correct misspelled word in footnote 7 to electrophoresis.

Lines 1134 – 1188: Along with PQITs, allowance should be made for sunset testing, where performance of a test will be terminated completely once an agreed number of sequential batches has been tested and all meet the acceptance criterion. The concept of the use of periodic quality indicators or skip testing is also covered in ICH Q6a. Both the ICH guideline and this document indicate that such tests can be implemented "where justified" but give no guidance on the approach or data requirements that might be used in the justification. To encourage companies to increase their process understanding by performing process capability studies consideration should be given to indicating in this guideline that process capability assessments may be used in supporting the justification.

Line 1204: Clarification of the term revision; perhaps version would be a better word.

Lines 1338-1339: Emphasis should be made on the outcome of the drug substance as a component of the drug product. Some attributes of the drug substance can be key to the performance of the drug product and it should be made clear here. Suggest to add a sentence "Additionally, studies on the properties of the drug product can assist in justifying the acceptance criteria for particular drug substance characteristics."

Lines 1360 – 1364: Require clarification because interim specifications for parameters which will not change on stability may be appropriate when a full stability package is not available at submission.

Lines 1519 – 1521: This text should be deleted to avoid defining any prescriptive requirements as regards TSE risk assessment criteria or supporting documentation requirements.

Lines 1632 – 1641: Delete text and cross-refer to appropriate comparability protocols guidance.

Lines 1688 – 1693: The statement that starting materials should have a "significant non-pharmaceutical market" is unjustified. As noted in lines 1679 to 1680, it is the quality of the starting material (and not its origin or its other uses) which determines suitability as an input to manufacture of drug substance. Materials with no non-pharmaceutical market are likely to be of higher quality and manufactured in superior facilities. They are therefore more suitable, not less suitable, as starting materials. This is acknowledged by FDA in lines 1700 to 1704, which refer to the possible need to purify materials, made for the non-pharmaceutical market.

Lines 1739 – 1750: Propinquity - The draft guidance indicates that several isolated synthetic steps must separate the starting material and drug substance. This could be problematic for: 1) Process Analytical Technology (PAT) approaches which minimize or eliminate isolation steps, 2) very short synthetic process with few or no isolation steps. Suggest specifying that this criterion is suggested, but amenable to discussion on a case by case basis.

The underlying premise for starting materials should be identity, quality, purity, and potency of the synthesized drug substance. Once assured through appropriate controls, the number of drug substance intermediates isolated or the location in the synthesis route (i.e., propinquity) becomes non-relevant.

Propinquity should be defined in terms of the number of purified intermediates between starting material and drug substance. Each purification by definition effects a reduction of impurity levels and an increase in quality. Isolation of the intermediate, for example, by crystallization is one method of purification but effectiveness may be limited by requirement to heat the crystallizing solution and to dry the crystalline product. Each of these can lead to degradation. Therefore intermediates demonstrably purified in solution (i.e., by an extractive work-up) should be counted when determining propinquity. Also conversion of a salt to its free acid or base form (or vice versa) can effect purification and should also be counted when determining propinquity.

The risk of a new impurity in the starting material being carried over to the drug substance should be controlled using a tight limit on “any unspecified impurity” in the specification of the starting material. Change the first sentence in this section to “A substance (or compound) proposed as a starting material may be separated from the final drug substance by several reaction steps that result in demonstrably purified intermediates.

Line 1769: The requirement that a starting material is “purified” suggests a mandatory purification step in its manufacture. This is unreasonable. Requirement should be for a well-defined impurity profile, ideally with a low limit for unidentified impurities (which may vary from one supplier to another or from the same supplier with time).

Lines 1776 – 1789: It is a reasonable expectation from FDA that starting materials should be of suitably high purity. However many starting materials (including those with significant non-pharmaceutical use) contain related substances at levels significantly in excess of 0.1% which carry through into impurities in drug substance at similar levels. Impurities in the starting materials may be the source of impurities in the drug substance provided the levels of those in the drug substance are qualified during development. The important factor is tight control of unspecified impurities in starting materials since these could give rise to unqualified impurities in drug substance. The inclusion of a specific limit of impurities is too prescriptive and should be deleted from the guidance. Sufficient toxicity coverage and the costs/yields associated with the removal of impurities from starting materials may render removal unwarranted. For example, a level of 0.1% of the opposite isomer in a naturally derived starting material (i.e., amino acid) may be acceptable, even if leading to 0.1% in the drug substance of the opposite enantiomer in the drug substance. Suggested text for lines 1776 to 1777 is “Impurities in a starting material should be specified individually, and derived impurities in drug substance should be qualified at levels justifying the acceptance criteria for impurities in the starting material. Inclusion of a low limit for unspecified impurities is recommended. Delete lines 1783 to 1789.

Lines 1791 – 1796: The draft guidance indicates that the starting material should be at or before the point in the manufacturing process where TSE agents could be introduced into the process. We suggest that the FDA guideline adopt the EU approach, whereby materials that are potential TSE agents introduced into the process before the starting material are documented/certified to be free from TSE. The requirement for TSE information is inappropriate and should be deleted from this guidance.

Lines 1801 – 1817: Clarity is needed on complexity of structure. The guidance states that if advanced techniques such as chiral HPLC are used to identify a starting material with a single chiral center, then the starting material could not be designated as a starting material. This should only relate to complex structures, as chiral HPLC is used as a purity determinant for the required isomer. Suggested text would be to add these sentences after the first two sentences in the section (lines 1800 to 1804). “...analogs. The specification for the starting material should contain identity and purity tests which clearly distinguish it from isomers and analogs that might reasonably be expected to be present in place of or as well as the desired compound. Distinction from compounds whose presence is purely theoretical (for example, enantiomers of steroids and other natural products) is not required.”

Lines 1830 – 1840: Delete this section as the information requested should not be part of registered detail.

Lines 1862 – 1866: Clarify the difference between proximity used here and propinquity used elsewhere in the guidance.

Lines 1870 – 1892: Delete this section, as applicants should not be responsible to report other uses of a starting material.

Lines 1927 – 1928: The impurity from a starting material is no worse than any other impurity. As long as the documentation has coverage for the impurity, it should not be set to a different level of detail/requirements in the document as suggested in the draft guidance. Suggested text to start this section is “Impurities in a starting material should be specified individually, and derived impurities in drug substance should be qualified at levels justifying the acceptance criteria for impurities in the starting material. Inclusion of a low limit for unspecified impurities is recommended.”

Lines 1976 – 1979: Delete these sentences because the information requested should not be part of the registered detail.

Lines 1993 – 2019: All organic compounds are ultimately derived from biological sources. It is not reasonable to regard any such sources as starting materials when they are extracted or similarly physically processed to yield highly purified and well-characterized substances used to manufacture semi-synthetic or totally synthetic drug substances.

FDA accepts that such substances may be acceptable as starting materials when they have significant non-pharmaceutical use. As noted earlier, this criterion is not scientifically justifiable. Therefore all such substances, regardless of use should be potentially acceptable as starting materials

The purified substances used to make semi-synthetic or totally synthetic drug substances should be controlled by specification.

It may be reasonable to regard the biological source as the starting material where the drug substance is derived with no chemical modification.

Suggested text for this section is to keep lines 1993 to 1997, followed by “The term *drug substance derived from a biological source* refers to drug substances which are obtained from the biological source without chemical modification”, and deleting the remainder of the section (lines 1997 to 2019).

Lines 2030 – 2052: The information required for the biological starting material is too detailed and onerous. The information required should be limited to that which is expected to have an impact on the quality of the derived drug substance.

Suggested text at the end of line 2030 is “The information required should be limited to that which is expected to have an impact on the quality of the derived drug substance.”

Lines 2107 – 2253: Add definitions for “Reprocessing” and “Reworking”. Suggested text is:

Reprocessing: Reprocessing is the introduction of an intermediate or drug substance, including one that does not conform to a standard or specification, back into the process and repeating a crystallization or other appropriate chemical or physical manipulations (e.g., distillation, filtration, neutralization/salt formation, chromatography, milling) that are part of the approved manufacturing process. Continuation of a manufacturing step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing.

Reworking: Reworking is subjecting an intermediate or drug substance that does not conform to a standard or specification to one or more manufacturing steps that are different from the manufacturing process described in the application to obtain acceptable quality intermediate or drug substance.

Lines 2121 – 2123: Critical process parameters are those having a narrow acceptable range, not just a defined range (which may be wide). Suggested text is to insert “narrow” between predetermined and criteria.

Line 2135: Incorrect sentence grammar. Suggested text is “...body. It does not...”

Line 2180: Polymorphic forms are not limited to drug substances. Delete the word “drug” in the first sentence of the definition.

Lines 2183 – 2192: “Postsynthesis material” is an unhelpful concept and should be abandoned. Delete this text.

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GENERAL COMMENTS

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Line 472: Clarity is needed on the inclusion of yield ranges.

Lines 474 - 483: "Derived from a biological source" and "biological starting material" are not meaningful terms. All organic compounds are ultimately derived from biological sources. Use suggested text for line 49. It is not justified to require this type of information for a semi-synthetic drug substance which results from chemical modification of a highly purified and well-characterized substance derived from plants or animals. Delete lines 478-483 unless well clarified.

Lines 488-491 and lines 1525-1527: The country of origin of a particular material of bovine origin is not the sole determinant of the risk of TSE transmission posed by that material. Other factors, such as tissue used, age of animal, processing, route of admin and dose are all thought to influence the potential risk. The fact that a material is bovine derived and originates from a BSE country as defined by USDA, does not necessarily mean that the material poses a risk of transmission. As written, the guideline would appear to prohibit the use of materials such as milk derivatives within manufacturing facilities if obtained from countries on the USDA list. However, milk derivatives are widely recognized as being safe, regardless of the country of origin. Similar arguments apply to other commonly used materials such as tallow derivatives, amino acids etc. that are considered to pose negligible risk of transmission due to the source tissues used, aggressive processing applied, or both. As noted under General Comments above, it is recommended that guidance on TSE risk minimization be removed from this guideline on the understanding that separate guidance is in preparation by FDA.

Lines 491-493 and 1510-1523: As stated under general comments above, the guideline would benefit from a clearer delineation between the requirements for products of chemical synthesis and those obtained from biological sources so far as guidance on adventitious agents safety is concerned. In particular, certain references are made in the document to the need to consider the risk of cross-contamination, and it is suggested that additional facilities information can be warranted under certain circumstances. It is understood that this is intended to only apply to biologics, but this is not entirely clear in places. To the extent that such requirements might be applied to products of chemical synthesis manufactured using highly processed reagents of animal origin, it is contended that the risk is negligible, and is appropriately handled through application of cGMP. As such, detailed facilities information, or information regarding other materials processed in the same facility, should not be required for such drug substances.

Line 500: Process Controls should be Header 3., not a bullet item.

Lines 514 – 516: Clarify or change the terminology of the two types of process tests. For example, change “in-process material tests” to “control of intermediates”.

Lines 520 – 521: Clarification is needed here. The applicant may choose to apply additional controls that are not registered. Suggested text would be “All process controls, necessary to ensure appropriate quality of the drug substance, should be included in the description of the manufacturing process.”

Lines 540 – 542: Clarification is needed here. Suggested text would be “All tests on intermediates and unfinished drug substance necessary to ensure appropriate quality, should be listed...” and “...in the flow diagram...” should be deleted.

Lines 565 - 618: This section covers reprocessing and reworking. Although the definitions are comprehensive they do not adequately address the issue of intermediate or API salt conversion back to the free base and then back to the same salt and whether it is considered reprocessing or reworking. Suggested text for lines 567-571 is to add neutralization/salt formation in the parenthetical clause so that the sentence reads "Reprocessing is the introduction of an intermediate or drug substance, including one that does not conform to a standard or specification, back into the process and repeating crystallization or other appropriate chemical or physical manipulations (e.g., distillation, filtration, neutralization/salt formation, chromatography, milling) that are part of the approved manufacturing process.

Line 636: Controls of recovered solvents (to a specification) is excessive and should be recovered as fit for purpose.

Lines 666 – 718: All organic compounds are ultimately derived from biological sources. It is not reasonable to regard any such sources as starting materials when they are extracted or similarly physically processed to yield highly purified and well-characterized substances used to manufacture semi-synthetic or totally synthetic drug substances. [It may be reasonable to regard the biological source as the starting material where the drug substance is derived with no chemical modification].

The purified substances used to make semi-synthetic or totally synthetic drug substances should be controlled by specification when used as starting materials. Later compounds in the synthetic sequence may be equally or more suitable as starting materials, particularly if their quality can be better controlled.

Where appropriate the applicant should present a risk assessment concerning control of pathogens, herbicides, pesticides etc. and, if necessary, demonstrate such control in the specifications. Details of the isolation and purification of such substances should not be required for this purpose. This information should be referenced to the appropriate attachment to avoid inconsistencies and duplication. In line 690, add “without chemical modification” after biological source, delete lines 693 – 694 since they duplicate lines 683 – 688, move lines 697 – 701 to line 707 and clarify that these lines also apply to semi-synthetic drug substances, the definition of in lines 701 – 704 should be in alignment with line 49, delete the sentence in lines 703 – 705, and delete lines 710 – 718 as it is defined in the appropriate attachment.

Line 676: Delete "For materials of biological origin,..."

Lines 754 – 761: This section refers to drug product, and should be deleted.

Line 774: Clarify the regulatory status of non-critical controls, both in respect to compliance with cGMP and also with respect to regulatory activity required if such controls are changed.

Lines 796 - 809: In ICH Q3C, it is acceptable to not test for a residual solvent if the levels are below the accepted limits in the materials used. For residual catalysts testing the same should apply, that is, if the level of the catalyst is controlled in one step it does not have to be tested in the subsequent step. It is frequently possible to demonstrate that levels of specific impurities are reduced when an intermediate is processed to drug substance. In such cases the requirement that the acceptance criterion should be identical or tighter in the intermediate is unreasonable. Suggested text is to add, "unless data are provided to justify a lower limit" at the end of sentence.

Line 817: When controls are applied for all reasonable impurities, testing for assay has no added value and should not be required. Delete "assay and" from the sentence.

Line 821: Definition of the substance used at the beginning of a semi-synthetic process, as an intermediate is unreasonable. Change "intermediate" to "substance" or "compound" in the sentence.

Lines 838 – 853: The concept of "postsynthesis materials" is not helpful. Delete this text.

Lines 895 – 896: Clarify the expectation for "Manufacturing changes associated with changes in the impurity profiles of intermediates should also be described".

Line 905: Delete the term "procedures".

Line 917: "Evidence for structure" would be a better term than "Elucidation of structure". Also clarify that not all tests are required for every drug substance and that discretion can be used to choose only the tests necessary to provide adequate evidence of structure.

Line 927: When exact mass is available from mass spectrum of drug substance, elemental analysis adds no value. It should only be required for salts for example.

Line 929: Only single crystal X-ray crystallography (not powder X-ray crystallography) can be used to provide evidence of structure. When single crystal X-ray data are available, no further confirmation of structure should be required. Change text appropriately.

Line 932 – 933: Please clarify meaning of “When the drug substance consists of more than one molecular species”. Does this refer to a drug substance, which is a mixture of close analogues, for example, a polyethyleneglycol ester? If so, the requirement to provide information on each component is unreasonably onerous and could be impossible.

Line 1008: Please clarify “potential impurities”. Confirm that they can be limited to impurities, which might reasonably be expected to be present.

Lines 1056 – 1057: Chemical and particularly physical properties of an impurity or potential impurity should not be required. Delete this bullet.

Line 1087: Delete text “in section” from sentence.

Lines 1087 – 1090: When unfinished drug substance is fully tested and drug substance itself undergoes limited testing, separation of the two specifications to S.2.4 and S.4.1 is not helpful.

Lines 1089 – 1090: Request clarification regarding drug substance specifications for mixtures of two or more drug substances. The draft guidance document implies that specifications must be presented for each individual drug substance, as well as subsequent mixtures of the drug substances. As written, the guidance refers to a specification for a combination of drug substances within the drug product. The wording is unclear.

Lines 1120 – 1122: Clarify the status of alternative analytical procedures, both in terms of compliance with cGMP and also in terms of regulatory requirements to change.

Line 1128 (Table 1): Change text in table in identification test (2) from spectra to spectrum and insert NMT in the acceptance criteria column for heavy metals (NMT 0.0001%). The table gives the impression that inclusion of both Infrared Absorption and HPLC retention time is required to confirm identity. A single specific identification (such as infrared testing) would normally be considered sufficient.

Line 1130 (Table 2): Correct misspelled word in footnote 7 to electrophoresis.

Lines 1134 – 1188: Along with PQITs, allowance should be made for sunset testing, where performance of a test will be terminated completely once an agreed number of sequential batches has been tested and all meet the acceptance criterion. The concept of the use of periodic quality indicators or skip testing is also covered in ICH Q6a. Both the ICH guideline and this document indicate that such tests can be implemented "where justified" but give no guidance on the approach or data requirements that might be used in the justification. To encourage companies to increase their process understanding by performing process capability studies consideration should be given to indicating in this guideline that process capability assessments may be used in supporting the justification.

Line 1204: Clarification of the term revision; perhaps version would be a better word.

Lines 1338-1339: Emphasis should be made on the outcome of the drug substance as a component of the drug product. Some attributes of the drug substance can be key to the performance of the drug product and it should be made clear here. Suggest to add a sentence "Additionally, studies on the properties of the drug product can assist in justifying the acceptance criteria for particular drug substance characteristics."

Lines 1360 – 1364: Require clarification because interim specifications for parameters which will not change on stability may be appropriate when a full stability package is not available at submission.

Lines 1519 – 1521: This text should be deleted to avoid defining any prescriptive requirements as regards TSE risk assessment criteria or supporting documentation requirements.

Lines 1632 – 1641: Delete text and cross-refer to appropriate comparability protocols guidance.

Lines 1688 – 1693: The statement that starting materials should have a "significant non-pharmaceutical market" is unjustified. As noted in lines 1679 to 1680, it is the quality of the starting material (and not its origin or its other uses) which determines suitability as an input to manufacture of drug substance. Materials with no non-pharmaceutical market are likely to be of higher quality and manufactured in superior facilities. They are therefore more suitable, not less suitable, as starting materials. This is acknowledged by FDA in lines 1700 to 1704, which refer to the possible need to purify materials, made for the non-pharmaceutical market.

Lines 1739 – 1750: Propinquity - The draft guidance indicates that several isolated synthetic steps must separate the starting material and drug substance. This could be problematic for: 1) Process Analytical Technology (PAT) approaches which minimize or eliminate isolation steps, 2) very short synthetic process with few or no isolation steps. Suggest specifying that this criterion is suggested, but amenable to discussion on a case by case basis.

The underlying premise for starting materials should be identity, quality, purity, and potency of the synthesized drug substance. Once assured through appropriate controls, the number of drug substance intermediates isolated or the location in the synthesis route (i.e., propinquity) becomes non-relevant.

Propinquity should be defined in terms of the number of purified intermediates between starting material and drug substance. Each purification by definition effects a reduction of impurity levels and an increase in quality. Isolation of the intermediate, for example, by crystallization is one method of purification but effectiveness may be limited by requirement to heat the crystallizing solution and to dry the crystalline product. Each of these can lead to degradation. Therefore intermediates demonstrably purified in solution (i.e., by an extractive work-up) should be counted when determining propinquity. Also conversion of a salt to its free acid or base form (or vice versa) can effect purification and should also be counted when determining propinquity.

The risk of a new impurity in the starting material being carried over to the drug substance should be controlled using a tight limit on “any unspecified impurity” in the specification of the starting material. Change the first sentence in this section to “A substance (or compound) proposed as a starting material may be separated from the final drug substance by several reaction steps that result in demonstrably purified intermediates.

Line 1769: The requirement that a starting material is “purified” suggests a mandatory purification step in its manufacture. This is unreasonable. Requirement should be for a well-defined impurity profile, ideally with a low limit for unidentified impurities (which may vary from one supplier to another or from the same supplier with time).

Lines 1776 – 1789: It is a reasonable expectation from FDA that starting materials should be of suitably high purity. However many starting materials (including those with significant non-pharmaceutical use) contain related substances at levels significantly in excess of 0.1% which carry through into impurities in drug substance at similar levels. Impurities in the starting materials may be the source of impurities in the drug substance provided the levels of those in the drug substance are qualified during development. The important factor is tight control of unspecified impurities in starting materials since these could give rise to unqualified impurities in drug substance. The inclusion of a specific limit of impurities is too prescriptive and should be deleted from the guidance. Sufficient toxicity coverage and the costs/yields associated with the removal of impurities from starting materials may render removal unwarranted. For example, a level of 0.1% of the opposite isomer in a naturally derived starting material (i.e., amino acid) may be acceptable, even if leading to 0.1% in the drug substance of the opposite enantiomer in the drug substance. Suggested text for lines 1776 to 1777 is “Impurities in a starting material should be specified individually, and derived impurities in drug substance should be qualified at levels justifying the acceptance criteria for impurities in the starting material. Inclusion of a low limit for unspecified impurities is recommended. Delete lines 1783 to 1789.

Lines 1791 – 1796: The draft guidance indicates that the starting material should be at or before the point in the manufacturing process where TSE agents could be introduced into the process. We suggest that the FDA guideline adopt the EU approach, whereby materials that are potential TSE agents introduced into the process before the starting material are documented/certified to be free from TSE. The requirement for TSE information is inappropriate and should be deleted from this guidance.

Lines 1801 – 1817: Clarity is needed on complexity of structure. The guidance states that if advanced techniques such as chiral HPLC are used to identify a starting material with a single chiral center, then the starting material could not be designated as a starting material. This should only relate to complex structures, as chiral HPLC is used as a purity determinant for the required isomer. Suggested text would be to add these sentences after the first two sentences in the section (lines 1800 to 1804). “...analogs. The specification for the starting material should contain identity and purity tests which clearly distinguish it from isomers and analogs that might reasonably be expected to be present in place of or as well as the desired compound. Distinction from compounds whose presence is purely theoretical (for example, enantiomers of steroids and other natural products) is not required.”

Lines 1830 – 1840: Delete this section as the information requested should not be part of registered detail.

Lines 1862 – 1866: Clarify the difference between proximity used here and propinquity used elsewhere in the guidance.

Lines 1870 – 1892: Delete this section, as applicants should not be responsible to report other uses of a starting material.

Lines 1927 – 1928: The impurity from a starting material is no worse than any other impurity. As long as the documentation has coverage for the impurity, it should not be set to a different level of detail/requirements in the document as suggested in the draft guidance. Suggested text to start this section is “Impurities in a starting material should be specified individually, and derived impurities in drug substance should be qualified at levels justifying the acceptance criteria for impurities in the starting material. Inclusion of a low limit for unspecified impurities is recommended.”

Lines 1976 – 1979: Delete these sentences because the information requested should not be part of the registered detail.

Lines 1993 – 2019: All organic compounds are ultimately derived from biological sources. It is not reasonable to regard any such sources as starting materials when they are extracted or similarly physically processed to yield highly purified and well-characterized substances used to manufacture semi-synthetic or totally synthetic drug substances.

FDA accepts that such substances may be acceptable as starting materials when they have significant non-pharmaceutical use. As noted earlier, this criterion is not scientifically justifiable. Therefore all such substances, regardless of use should be potentially acceptable as starting materials

The purified substances used to make semi-synthetic or totally synthetic drug substances should be controlled by specification.

It may be reasonable to regard the biological source as the starting material where the drug substance is derived with no chemical modification.

Suggested text for this section is to keep lines 1993 to 1997, followed by “The term *drug substance derived from a biological source* refers to drug substances which are obtained from the biological source without chemical modification”, and deleting the remainder of the section (lines 1997 to 2019).

Lines 2030 – 2052: The information required for the biological starting material is too detailed and onerous. The information required should be limited to that which is expected to have an impact on the quality of the derived drug substance.

Suggested text at the end of line 2030 is “The information required should be limited to that which is expected to have an impact on the quality of the derived drug substance.”

Lines 2107 – 2253: Add definitions for “Reprocessing” and “Reworking”. Suggested text is:

Reprocessing: Reprocessing is the introduction of an intermediate or drug substance, including one that does not conform to a standard or specification, back into the process and repeating a crystallization or other appropriate chemical or physical manipulations (e.g., distillation, filtration, neutralization/salt formation, chromatography, milling) that are part of the approved manufacturing process. Continuation of a manufacturing step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing.

Reworking: Reworking is subjecting an intermediate or drug substance that does not conform to a standard or specification to one or more manufacturing steps that are different from the manufacturing process described in the application to obtain acceptable quality intermediate or drug substance.

Lines 2121 – 2123: Critical process parameters are those having a narrow acceptable range, not just a defined range (which may be wide). Suggested text is to insert “narrow” between predetermined and criteria.

Line 2135: Incorrect sentence grammar. Suggested text is “...body. It does not...”

Line 2180: Polymorphic forms are not limited to drug substances. Delete the word “drug” in the first sentence of the definition.

Lines 2183 – 2192: “Postsynthesis material” is an unhelpful concept and should be abandoned. Delete this text.