

July 1, 2004

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

Re: **Docket No. 2003D-0571**, Draft FDA Guidance “Drug Substance Chemistry, Manufacturing, and Controls Information”

Eli Lilly and Company is pleased to have the opportunity to comment on the subject draft document.

We believe that some sections of this draft guidance are inconsistent with the Agency’s Quality by Design and Risk Management Initiatives. We fully support those initiatives and we have provided suggestions herein to align the guidance more closely with the philosophy embodied in those initiatives.

Attached below are Eli Lilly comments on the draft guidance. Key Points are presented first, followed by General Comments and then a table of Detailed Comments.

Please feel free to contact me at (317) 433-9882 for clarification of any comments.

Sincerely,



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**Eli Lilly and Company Comments on:  
Draft FDA Guidance “Drug Substance Chemistry, Manufacturing, and Controls  
Information” (Docket No. 2003D-0571; January 7, 2004)**

**Key Points:**

1. In numerous places through the draft guidance, the phrase “all process controls” is used. These statements need to be revised to read “all critical process controls”. The inclusion of only those process controls determined to be critical is consistent with the Quality by Design and Risk Management Initiatives. Inclusion of “all” process controls is an unnecessary level of detail, which will result in increased burden on the industry and FDA reviewers with no added value. Providing critical controls (consistent with the definition provided in the draft guidance glossary) and information supporting the design of the process in either section S.2.4 Control of Critical Steps and Intermediates or S.2.6 Manufacturing Process Development will together provide the information needed to assess the adequacy of the process described.
  
2. Starting Materials: The entire Attachment 1 in the Draft Guidance should be substantially rewritten with a science- and risk-based approach. We support the following statements in the draft guidance and believe any criteria proposed should be consistent with that philosophy:  
“FDA will consider the justification provided to support a proposed starting material as well as other relevant information such as the proposed starting material specification and controls on manufacturing steps downstream from the proposed starting material when evaluating the appropriateness of a proposal to designate a chemical as a starting material.”... “These principles are intended to assist an applicant in proposing starting materials at a point in the process that ensures the following:
  - ?? Sufficient information is submitted in the application for FDA to evaluate the safety and quality of the drug substance;
  - ?? Future changes in the manufacture of the starting material are unlikely to affect the safety or quality of the drug substance.”

Many of the criteria proposed for starting materials in the FDA draft guidance are inappropriate and inconsistent with the above statements. Specifically, we have the following comments:

- a. We suggest that the agency abandon the categorization of “with/without significant non-pharmaceutical market” along with any criteria related to commercial availability for the following reasons:
  - ?? As stated above, the key concept in defining a starting material is that the starting material specification and downstream process controls ensure the quality and safety of the drug substance. The use of a chemical outside of the pharmaceutical industry does not address this key concept.
  - ?? A vast majority of chemicals which are appropriate to designate as starting materials for the drug substances covered by this guidance would fall under the category of “materials without a significant non-pharmaceutical market” (as defined in this draft guidance). The FDA has applied unnecessarily stringent criteria to this majority of materials with no scientific justification for the disparate requirements.
  - ?? Determination of whether a significant non-pharmaceutical market exists may be difficult for a pharmaceutical manufacturer to determine.

?? A number of chemicals which are common building blocks for pharmaceuticals but do not have a “significant non-pharmaceutical market” can be controlled by the same requirements appropriate for chemicals with a significant non-pharmaceutical market. Examples are phenylglycine salts, materials closely related to commodity chemicals, and materials that are chemically simple and easily prepared that do not happen to have a non-pharmaceutical market.

b. We have significant concerns about the criteria proposed for materials without a significant non-pharmaceutical market. As noted above, we believe the FDA should develop criteria with sufficient flexibility for any potential starting material. Regardless of whether the FDA adopts that approach or not, we have strong concerns that the FDA may utilize the criteria proposed for materials without a significant non-pharmaceutical market as the basis of any final recommendation. We therefore have outlined the most significant of our concerns about these criteria here, and the more detailed points are provided in the table of line-by-line comments.

- ?? Propinquity- Number of steps: The requirement for a starting material to be separated from the final intermediate by several reaction steps is inconsistent with existing FDA guidance and is scientifically unnecessary. A fundamental BACPAC principle is that changes prior to the final intermediate are low risk. BACPAC 1 provides for the redefinition of an intermediate (except for the final intermediate) as a starting material in a CBE-30. Therefore, it is inconsistent to require a starting material to be several steps prior to the step that has previously been stated as a point where changes are low risk. A more scientifically appropriate requirement is the following: “A chemical proposed as a starting material should be separated by a sufficient number of steps to ensure drug substance quality”. This provision allows for the scientific flexibility necessary to address a vast array of chemical syntheses and the corresponding array of control strategies appropriate for each synthesis.
- ?? Propinquity- Definition of “reaction steps”: The definition of reaction step contained in lines 1741-1742 and 1753-1757 is inconsistent with the definition in the glossary. In addition, subsequent purification steps should in fact be considered in evaluating the appropriateness of a starting material. Purification steps do serve to reduce the risk which could be present from any changes in the starting material impurity profile.
- ?? Carryover of impurities: The first line should be revised to read “a chemical proposed as a starting material should not be the source of significant levels of *unspecified* impurities in the drug substance”. Lines 1784 through 1790 should be deleted. As long as the impurities in the drug substance are identified and qualified, the source of those impurities is irrelevant. Eliminating a chemical as a starting material merely because it contributes a known and qualified impurity has no scientific basis. The limit of 0.10 percent is the ICH identification threshold, and its relevance in this context is unclear.
- ?? Complexity: The restrictions related to complexity are unnecessary and irrelevant. If the proper controls are in place using appropriately validated analytical techniques (i.e. have sufficient sensitivity and selectivity), the number of isomers or chiral centers is irrelevant. The requirement that starting materials must be able to be controlled by simple, archaic techniques has no scientific basis. We note that many of the techniques provided as examples of “advanced techniques” are actually routine techniques (e.g. proton NMR, chiral HPLC). Also, UV and IR are used for identity testing and not structure elucidation as implied.

- ?? Documentation- Flow Diagram: The guidance requires the synthesis flow diagram to begin with chemicals that have a significant non-pharmaceutical market, most likely prior to starting material designation. This requirement is in conflict with the rationale that starting materials can be sourced from different vendors with potentially different routes of manufacture since the downstream impurity control strategy is in place. This whole section (Lines 1831-1841) should be eliminated. Instead, the flow diagram should begin with the appropriately justified starting material.
- ?? Specifications: Data used to determine appropriate specifications for starting materials can include impurity spiking studies in addition to historical batch analyses of starting material lots used.
- ?? Criteria are guidelines: The guidance should be revised to clearly state that the criteria listed are guidelines and that failure to meet a criterion does not necessarily preclude defining a compound as a starting material. However, the rationale for starting material selection must be provided.

### **General comments:**

1. In a number of places reference is made to non-yet-published guidance documents. It is inappropriate to refer applicants in this draft to unpublished guidance.
2. Naturally derived protein drug substances should be removed from the scope of this guidance. The inclusion of proteins leads to confusion in multiple sections since the manufacture, control strategy, and testing of proteins are significantly different from drug substances manufactured by chemical synthesis.
3. The introduction of the guidance provides a listing of drug substance types for which the guidance does not provide specific recommendations. It states that applicants for those products “can apply the content recommendations in this guidance, as scientifically appropriate”. But, later in the background information, the guidance suggests that applicants refer to a number of other guidance documents (lines 169-180) for specific technical issues. The list of guidances is in fact for products not specifically covered by this guidance. Therefore, it is unclear to what extent applicants for the substance types not covered are expected to follow this guidance. Is the intent primarily that applicants for those substances follow the CTD format demonstrated?
4. After a number of sections a box containing references is provided. We suggest that references are simply provided at the end of the document. The references provided often provide little guidance relative to the section presented, and most of the references are the same for each section.
5. The inclusion of the following concepts in this guidance is welcomed. These concepts acknowledge the continued learning that will occur for the registered product in the post-approval phase, facilitate communication between industry and FDA, and provide additional registration flexibility.
  - ?? PAT (lines 512-514)
  - ?? Tests in lieu of drug substance tests (lines 795-812)
  - ?? Sunset testing (lines 1110-1111, 1314-1333)
  - ?? Interim specifications (lines 1110-1111, 1347-1366)
  - ?? Periodic quality indicator tests (lines 1135-1188)
  - ?? Comparability protocols for post-approval changes (lines 1632-1641)
6. The clarification of registration requirements for reprocessing and reworking is very helpful.

**Detailed Comments:**

Section	Guidance Line	Comment	Rationale
	Page 6-8 Master Files	It is suggested that information be presented in the marketing application which is redundant with that in a referenced master file. Those redundant requirements should be deleted.	Maintenance of duplicated information in the application is unnecessary and creates a maintenance burden for industry and an additional review burden for FDA reviewers.
General Properties (S.1.3)	352	<p>Biological activities should be added to the list specific to naturally derived protein drug substances on lines 357 to 359, and qualified on line 352 for synthetic drug substances as follows:</p> <p>Biological activities (<i>for synthetic peptides</i>)</p>	Protein drug substances are tested for biological potency, but most drug substances manufactured by chemical synthesis are not.
IV. Manufacture (S.2)	379	<p>Revise from:</p> <p>...that will be involved in the manufacturing or testing of the drug substance.</p> <p>To:</p> <p>...that will be involved in the manufacturing or testing of <i>intermediate, post-synthesis materials, unfinished drug substance</i>, and the drug substance...</p>	Clarification. Section S.2 should also include sites where intermediates, post-synthesis materials, and unfinished drug substances are manufactured and tested.

Section	Guidance Line	Comment	Rationale
	383-384	<p>Revise to:</p> <p>Building numbers or other specific identifying information should be provided for multifacility campuses <i>for sterile processing of sterile drug substances</i>.</p>	<p>Building numbers should be required only for sterile/aseptic operations.</p> <p>According to <i>Changes to an Approved NDA or ANDA</i>, moving between buildings within a site does not have to be reported except for sterile/aseptic processing of sterile drug substances. Therefore, including building numbers in the initial application is unnecessary in most instances.</p>
	387-388	<p>Remove the following:</p> <p>...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.</p>	<p>The name, address, and phone number of the U.S. agent should not be required within the body of the application.</p> <p>This information is available in the 356H form and not appropriate for the body of the application.</p>
	390-392	<p>Remove the following:</p> <p>To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application.</p>	<p>The name, telephone number, fax number and e-mail address of a contact person should not be required within the body of the application.</p> <p>Contact information is available in the 356H form. Providing administrative information such as this in the body of the application is inconsistent with global harmonization as well.</p>
	392-393	<p>Remove the following:</p> <p>Facilities should be ready for inspection when the application is submitted to FDA.</p>	<p>This information is not pertinent to the content of the application and represents a new policy relative to pre-approval readiness which is inappropriate here.</p>

Section	Guidance Line	Comment	Rationale
	406-436	<p>1. Revise line 425 as follows:</p> <p><i>Critical</i> solvents, reagents, and auxiliary materials used in each manufacturing step</p> <p>2. Remove lines 427 and 431</p>	<p>Too much detail is suggested for inclusion in the Flow Diagram. Inclusion of all solvents, reagents, and auxiliary materials, operating parameters, and yields in general would not be appropriate for a general schematic overview</p> <p>The Flow Diagram should be a presentation of the synthetic scheme and key elements of the process which together provide a general overview of the process. The details of the process are provided in the narrative description.</p>
	441	<p>Revise to:</p> <p>...the scale of production should be provided <i>for the final step of the process</i>.</p>	<p>Scale changes are not reportable for steps up to the final intermediate per BACPAC 1.</p>

Section	Guidance Line	Comment	Rationale
	443 457 521-522 538	Revise from: “all process controls” To: “all critical process controls”  Note: This comment applies to numerous places throughout the guidance.	<p>The use of the term all is too inclusive. For example, control tests may be run</p> <ul style="list-style-type: none"> <li>?? to ensure process safety (e.g. confirm absence of water prior to adding a moisture-sensitive reagent)</li> <li>?? on a limited basis to monitor a reaction.</li> <li>?? to determine losses to mother liquor.</li> </ul> <p>The inclusion of only those process controls determined to be critical is consistent with the Quality by Design and Risk Management Initiatives. Inclusion of “all” process controls is an unnecessary level of detail, which will result in increased burden on the industry and reviewers with no added value. Providing critical controls (consistent with the definition provided in the draft guidance glossary) and information supporting the design of the process in either section S.2.4 Control of Critical Steps and Intermediates or S.2.6 Manufacturing Process Development will together provide the information needed to assess the adequacy of the process described.</p>

Section	Guidance Line	Comment	Rationale
	452-453	<p>Revise from: Solvents, reagents, and auxiliary materials used in each step, with chemical or biological names and quantities specified.</p> <p>To:</p> <p>Solvents, reagents, and auxiliary materials used in each step, with chemical or biological names and <i>reaction stoichiometry</i> specified.</p>	Reaction stoichiometry can be defined using molar equivalents and solvent volumes rather than exact quantities.
	454-455	<p>Revise from: Type of equipment (e.g., Centrifuge) used, including materials of construction when critical</p> <p>To:</p> <p>Type of equipment used, <i>where critical</i>.</p>	Equipment changes are not reportable for steps up to the final intermediate per BACPAC 1.
	466-467	<p>Revise from: Identification of manufacturing steps that use recovered solvents or auxiliary materials (see section IV.B.3.c)</p> <p>To:</p> <p>Identification of manufacturing steps that use <i>recycled</i> solvents or auxiliary materials (see section IV.B.3.c).</p>	<p>Recycled solvents/reagents are those reused in the process without purification. Therefore, designating where recycled materials are used is appropriate.</p> <p>Recovered solvents/reagents are purified such that they meet the same specifications as for new material as described in Section S.2.3, Control of Materials. Therefore, distinguishing the place where these materials are used is unnecessary.</p>

Section	Guidance Line	Comment	Rationale
	471-472	Revise from:  Identification of processes that involve combining intermediate or drug substance batches, drug substance and a diluent, or two or more drug substances  To:  Identification of processes that involve <i>blending drug substance batches, combining a drug substance and a diluent, or blending two or more drug substances.</i>	These lines should be qualified to allow for the typical processing which utilizes more than one intermediate batch into subsequent steps.
	473	Revise from: Yield ranges (weight and percent) for each manufacturing step  To:  <i>Expected</i> yield (weight and/or <i>molar</i> percent) for each manufacturing step	Yields given as a molar percent provide the same information on reaction completeness as those given as a weight.
	479, 480, 483	Delete these 3 points.	These 3 bullet points represent GMP operations which are unnecessary details for the marketing application

Section	Guidance Line	Comment	Rationale
	510-511	<p>Revise from: Environmental controls — conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)</p> <p>To:  Environmental controls— conditions associated with the manufacturing facility <i>for sterilization of sterile drug substances</i> (e.g., temperature, humidity, clean room classification)</p>	Environmental Controls for non-sterile operations are GMP operations not appropriate for inclusion in the application.
	527-536	Remove these examples.	The parameters given are often non-critical to the process; therefore, they would not be disclosed in the registration. It is the responsibility of the manufacturer to determine what parameters are critical to the process and describe that rationale in section S.2.4 Control of Critical Steps and Intermediates or S.2.6 Manufacturing Process Development.
	541-543	Remove the word “all” from the sentence beginning “All tests ....”.	The use of the term “all” is too inclusive. Tests may be run on a limited basis to gain additional information and be discontinued prior to NDA submission.
	545	<p>Add the following statement.</p> <p>Operating conditions may occasionally deviate from the NDA description. The manufacturer should document and explain any deviation. Any critical deviation should be investigated. Occasional, minor deviations need not be reported to the NDA.</p>	The statement regarding minor deviations in the 1987 guidance is no longer present. Industry would like clarification that the investigation of deviations is covered under GMPs and is not a registration issue.
	547-549	Remove the use of shadow print.	The diagram is difficult to read.

Section	Guidance Line	Comment	Rationale
	547-549	Delete the phrase “if critical” from Figure 1.	Non-critical controls should not be included.
	557-560	<p>Revise from:</p> <p>Information (e.g., comparative analytical data) to support the appropriateness of these operations should be included in S.2.2 or can be cross-referenced in S.2.2 if information is provided elsewhere in the application.</p> <p>To:</p> <p>Information (e.g. comparative analytical data) to support the <i>use of reworking, recycling, regeneration, and salvaging</i> operations should be included in S.2.2 or can be cross-referenced in S.2.2 if information is provided elsewhere in the application.</p>	Clarification of the information to be included.
	567-576 602-605	Definitions for reworking and reprocessing should be added to the glossary. We support the definitions provided in the text.	Clarification.
	578-579, 605-609	<p>Remove the following statement:</p> <p>Repetition of multiple reaction steps is considered to be reworking, rather than reprocessing.</p>	Repeating multiple steps should be considered reprocessing, consistent with ICHQ7A and acceptable practice.
	579	<p>Add the following at the end of this paragraph:</p> <p>Non-chemical unit operations which are not part of the routine processing can be conducted during reprocessing. Examples include dissolution in the routine solvent and filtration after dissolution.</p>	These operations do not introduce new chemical steps or reagents to the operation and are low risk.

Section	Guidance Line	Comment	Rationale
	584-587	<p>Delete this sentence:</p> <p>However, if there is a significant potential for the reprocessing operation to adversely affect the identity, strength, quality, purity, or potency of the drug substance, the reprocessing operations should be described and justified in this section (S.2.2) of the application.</p>	<p>Since reprocessing is a repeat of the established and registered process, it is unclear when reprocessing would have a significant adverse impact on the quality of the drug substance.</p>
	611-613	<p>Revise from:</p> <p>In general, reworking operations are developed postapproval, and the application is updated through submission of a prior approval supplement....</p> <p>To:</p> <p>In general, reworking operations are developed postapproval, and the application is updated through <i>the appropriate reporting mechanism</i> .....</p>	<p>Designation of post-approval requirements is contained in other guidance. Maintenance of redundant information in this document is unnecessary. Furthermore, the reporting category given is incorrect for intermediates up to and including the final intermediate as per BACPAC 1.</p>

Section	Guidance Line	Comment	Rationale
	628-637	<p>Replace the entire paragraph with the following sentence.</p> <p>The use of <i>recycled</i> solvents/reagents, including the point at which they might be used in the process, should be included in the description of the manufacturing process.</p>	<p>As noted above, recycled solvents/reagents are those reused in the process without purification. Therefore, designating where recycled materials are used is appropriate.</p> <p>Recovered solvents/reagents are purified such that they meet the same specifications as for new material as described in Section S.2.3, Control of Materials. Therefore, distinguishing the place where these materials are used is unnecessary. Given that the processing used to produce raw materials and solvents is not described, neither would the processing used to recover such materials.</p>
Control of Materials (S.2.3)	675-677	<p>Revise from:</p> <p>When appropriate, specific tests and acceptance criteria to control microbial contamination should be included in the specification for materials used to manufacture drug substances.</p> <p>To:</p> <p>Specific tests and acceptance criteria to control microbial contamination should be included in the specification for materials used to manufacture <i>sterile</i> drug substances.</p>	<p>Clarification. Microbial control for starting materials, reagents, solvents, auxiliary materials, and diluents is important for the control of sterile drug substances.</p>

Section	Guidance Line	Comment	Rationale
	683-695	Remove distinction between “API starting material” and “starting material”.	This paragraph attempts to distinguish definitions for “starting material” and “API starting material”. While FDA is delineating different <u>criteria</u> for the drug substance/API starting material than Q7A, attempting to create new terminology to address those different criteria is confusing. The terms mean the same thing, only the criteria presented is different.
	697 1668-1669 2234-2235	<p>Revise the definition of starting material from:</p> <p>Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance.</p> <p>To:</p> <p>A starting material for a synthetic drug substance is a chemical compound of defined molecular structure <b><i>that is incorporated as a significant structural fragment</i></b> into the structure of the drug substance.</p>	<p>Clarification, and consistency with ICHQ7A. The previous, 1987 guidance also included the concept that the starting material is an important structural element of the drug substance. We propose using the word fragment instead of element because the word <i>element</i> may also refer to the Periodic Table of Elements (e.g., carbon, hydrogen, oxygen, etc.), and therefore may be confusing.</p>
	739	<p>Revise from:</p> <p>The specification sheet should list all tests to which the material will conform and the....</p> <p>To:</p> <p>The specification sheet should list <b><i>critical</i></b> tests to which the material <b><i>must</i></b> conform and the....</p>	<p>The use of the term “all” is too inclusive. Raw materials are often used in multiple processes (in multiple NDAs), each of which may have special requirements. Each NDA should register those tests that control the quality of that particular drug substance.</p>

Section	Guidance Line	Comment	Rationale
	769-772	<p>Revise from:</p> <p>In this section of the application, all critical operating parameters, environmental controls, process tests and all tests performed on intermediates, postsynthesis materials, and unfinished drug substance should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified.</p> <p>To:</p> <p>In this section of the application, all critical <i>process controls</i> should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified.</p>	<p>a. Environmental controls are critical only for sterilization steps.</p> <p>b. “All” tests is too inclusive. Tests may be run on a limited basis to gain additional information and be discontinued prior to commercial production.</p>
	772-777	Remove these sentences.	It is unclear why non-critical tests for intermediates through drug substance would be included in the application.
	780	<p>Revise from:</p> <p>Any experimental data to support the justification should be included in this section (S.2.4) as well.</p> <p>To:</p> <p>Experimental data to support the justification should be included in this section (S.2.4) as well.</p>	<p>The use of the term “any” is too inclusive for two reasons.</p> <p>?? Early experimental studies may have been performed before a test was recognized as critical; therefore, these early studies may not have been performed under full GMP and be unsuitable for inclusion in a submission.</p> <p>?? A data summary, instead of detailed, raw data is more appropriate for submission.</p>

<b>Section</b>	<b>Guidance Line</b>	<b>Comment</b>	<b>Rationale</b>
	819 850 861-862	These 3 sentences should be clarified by the addition of the statement: “At a minimum, the reference should identify the type of analytical procedure used (e.g., GC, HPLC).”	Clarification to note that only method type need be specified. Specification, as defined by ICH, implies reference to a specific analytical procedure.
	877 Footnote 15	The following sentence should be revised from:  All manufacturing processes should be validated.  To: All critical manufacturing steps should be validated.	This is consistent with the concept that critical manufacturing process steps should be validated (re., lines 414, 456).
	895	Remove the phrase “or manufacturing site”	The site alone has no relevance here. Only the manufacturing process and associated changes should be discussed here.
	896-897	Delete the sentence “Manufacturing changes associated with changes in the impurity profiles of intermediates should also be described.”	Changes during development that impact only intermediate profiles may not be relevant to the impurity profile of the drug substance. The focus should be on significant changes, therefore those that have impacted the drug substance.
Characteriza-tion (S.3)			
Elucidation of Structure and Other Characteristics (S.3.1)	Line 959	Remove the phrase “particle size analysis”	Particle size is not an inherent property of the drug substance. Particle size analysis should be taken out of this section and discussed in the justification for the drug substance specification (S.4.5) or in the physicochemical and biological properties section (P.2.2.3).
Impurities (S.3.2)	1007	Remove the space in the word “impurities”.	Typographical error.

Section	Guidance Line	Comment	Rationale
	1037	<p>Revise from:</p> <p>Attempts should be made to identify all impurities found in significant quantities in the drug substance.</p> <p>To:</p> <p>Attempts should be made to identify all impurities found <i>above the ICH identification threshold</i> in the drug substance.</p>	Consistency with ICH Q3A (R).
	1038	<p>Remove the following sentence:</p> <p>The studies to characterize these impurities should be described.</p>	Subsequent bullet points in lines 1049- 1065 define the information that should be provided.
	1052-1053	<p>Revise from:</p> <p>Analytical procedure used to detect or search for the impurity or potential impurity</p> <p>To:</p> <p>Analytical <i>technique</i> used to detect or search for the impurity or potential impurity</p>	The analytical technique (e.g. LC/MS) should be indicated, but not the detailed analytical procedure.
	1057-1058	<p>The point below should be deleted.</p> <p>Structural characterization data and/or other data on the physical or chemical properties of the impurity or potential impurity</p>	Additional scientific knowledge of the process and its control reduces the risk of future changes. However, this additional information is unrelated to scientific knowledge of the process and, therefore, contributes little to the registration.

Section	Guidance Line	Comment	Rationale
	1059-1060	<p>This point below should be deleted.</p> <p>Summary of the route of synthesis or method of preparation if the impurity or potential impurity was independently prepared</p>	<p>Additional scientific knowledge of the process and its control reduces the risk of future changes. However, this additional information is unrelated to scientific knowledge of the process and, therefore, contributes little to the registration.</p>
Control of Drug Substance (S.4)			
Specification (S.4.1)	1111-1114	<p>Revise from:</p> <p>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).</p> <p>To:</p> <p><b><i>In cases where the applicant and the drug substance manufacturer are different parties,</i></b> 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).</p>	<p>The requirement to specify which tests will be accepted based on a COA and which will be performed by the drug product manufacturer should be clarified such that this applies only to drug substances supplied by a third party. When the drug substance manufacturer is part of the same company, this requirement has no relevance.</p>

Section	Guidance Line	Comment	Rationale
Batch Analysis (S.4.4)	1257-1259	<p>Revise from:</p> <p>We discourage the use of terms such as <i>conforms</i> or <i>meets specification</i>.</p> <p>To:</p> <p>We discourage the use of terms such as <i>conforms</i> or <i>meets specification</i> <b>except when it is clear what specification the test results have been assessed against (e.g. description, identity, and limit tests).</b></p>	Use of terms such as “conforms” or “meets specification” should be appropriate when it is clear what specification the test results have been assessed against.
	1263	The word “all” should be deleted.	<p>The word all is too inclusive.</p> <p>?? Re-evaluation testing is often performed on early batches prior to the development of a stability profile. At the time of registration the stability profile is well defined in section S.7 (Stability).</p> <p>?? Tests may be performed on a limited number of batches to confirm the absence of suspected impurities. This data is already provided in section S.3.2 (Impurities).</p>

Section	Guidance Line	Comment	Rationale
	1267	<p>The following sentence should be revised from:</p> <p>A summary of any changes in the analytical procedures should be provided if the analytical procedures...</p> <p>To:</p> <p>A summary of <i>changes in analytical procedures that affect the reported result(s)</i> should be provided if the analytical procedures...</p>	<p>Changes in analytical procedures that affect the reported result should be described in this section. However, minor or editorial changes should not.</p>
	1280-1284	<p>Move the Collated Batch Analyses Data requirement to section S.4.5 Justification of Specification:</p>	<p>Since the collated data are used to assess the drug substance specification, section S.4.5 is a better location for this information.</p>
Justification of Specification (S.4.5)			
	1322-1323  1351	<p>Remove “scale, equipment”</p>	<p>Scale and equipment are given as examples for a difference in a manufacturing process which could produce uncertainty about the appropriateness of the specification. Scale or equipment changes alone should not generally be considered as impacting the quality of the drug substance.</p>

Section	Guidance Line	Comment	Rationale
	1372-1373	<p>Revise the following sentence from:</p> <p>Acceptance criteria for residual solvents should generally be based upon manufacturing capability.</p> <p>To:</p> <p>Acceptance criteria for residual solvents should be based on safety (per ICH Q3C and VICH GL18), analytical variability, and manufacturing variability.</p>	<p>At the time of submission, it is unusual to have manufactured enough batches to assess manufacturing capability. ICH Q3C and VICH GL18 provide guidance on safe levels of residual solvents. Analytical variability should also be considered when setting specifications.</p>
Reference Standards or Materials (S.5)			
	1395	<p>Revise from:</p> <p>Information on the reference standards or reference materials used for testing of the drug substance (active moiety) should be provided.</p> <p>To:</p> <p>Information on the <i>primary</i> reference standards used for testing of the drug substance (active moiety) should be provided.</p>	<p>Secondary standards which are assessed against the primary standard are covered under internal GMP controlled procedures.</p>

Section	Guidance Line	Comment	Rationale
	1397-1398	<p>The following sentence should be revised from:</p> <p>When the reference standard is not from an official source it should be fully characterized</p> <p>To:</p> <p>When the <i>drug substance</i> reference standard is not from an official source, it should be fully characterized.</p>	Clarification.
	1401-1402	<p>The following sentence should be revised from:</p> <p>A list of any available reference standards for impurities and intermediates should be included in S.5</p> <p>To:</p> <p>A list of <i>impurity reference standards that are referenced in drug substance analytical procedures</i> should be included in S.5</p>	Clarification. Residual intermediates in the drug substance are considered impurities.
Container Closure System (S.6)			

Section	Guidance Line	Comment	Rationale
	1414-1417	<p>The following sentence should be revised from:</p> <p>The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to the container and leaching, and/or safety of materials of construction.</p> <p>To:</p> <p>The suitability of the container closure system should be discussed with respect to compatibility and safety of the primary packaging components(s) and protection from moisture and light, if appropriate. A reference to the appropriate indirect food additive regulation is typically considered sufficient to establish the safety of the materials of construction.</p>	Consistency with the FDA Guidance <i>Container Closure Systems for Packaging Human Drugs and Biologics</i> (May 1999)
	1418	<p>The following statement should be added.</p> <p>Smaller versions that simulate the actual container closure system may be used in stability studies.</p>	Both the FDA guidance <i>Container Closure Systems for Packaging Human Drugs and Biologics</i> (May 1999) and ICH Q1A (R2) provide for the use of simulators. However, it would be helpful to include the information in this guidance for completeness.
<b>Stability Data (S.7.3)</b>			

Section	Guidance Line	Comment	Rationale
	1431	Revise from ..., shelf life acceptance criteria, .... to ..., shelf life/retest period acceptance criteria, ...	The term retest period is applicable for most drug substances. Shelf life implies an expiration date, which is not widely applied.
	1482-1483	The following statement should be revised from:  Stability data to support holding times for intermediates or during processing should also be provided in this section when warranted (e.g. certain proteins).  To:  Stability data to support holding times during processing should be provided in this section for proteins, if appropriate.	For drug substances manufactured by chemical synthesis, specifications, including tests for assay and impurities, are established for intermediates. These specifications ensure that the intermediate is fit for use in the subsequent step.
	1490-1491	Revise from:  Any results from drug substance stress testing....  To:  Results from drug substance stress testing....	The word “any” should be deleted from this sentence. Results should be provided for the stress studies as described in ICH Q1A (R2).

Section	Guidance Line	Comment	Rationale
Appendices (A)	1505	<p>Revise from:</p> <p>...(e.g., A.1 drug substance then drug product, followed by A.2).</p> <p>To:</p> <p>...(e.g. A.1.1 drug substance, A.1.2 drug product, A.2.1 drug substance, A.2.2 drug product).</p>	Clarification
Adventitious Agents Safety Evaluation (A.2)	1571-1574	Delete these lines.	Again the guidance is inconsistent in providing guidance to applicants of biotechnology-derived protein drug substances when this guidance is not intended for such drug substances.
Attachment 1: Starting Materials			
	1759	<p>Revise the sentence from:</p> <p>Isolated and purified intermediates are typically obtained by filtration or centrifugation, fractional distillation from a mixture, or chromatographic procedures.</p> <p>To:</p> <p>Isolated and purified intermediates are typically obtained by <b>crystallization</b>, fractional distillation from a mixture, or chromatographic procedures.</p>	Crystallization conditions determine impurity rejection into the mother liquor. Filtration and centrifugation are simply techniques for removing the mother liquor from the isolated crystals.

Section	Guidance Line	Comment	Rationale
	1764-1766	<p>Remove the phrase noted below:</p> <p>For example, evaporating solvent from a reaction mixture <del>or the extraction work up of a reaction mixture</del> is not considered to produce an isolated and purified intermediate.</p>	Extractions do provide purification. In addition, it is possible to have a purified material in solution.
	1828	<p>Revise this sentence as noted:</p> <p>The chemical name, CAS Registry Number, structure, molecular formula, molecular weight, <del>and relevant physical characteristics (e.g., appearance, physical state, melting or boiling range)</del> should be provided for each proposed starting material.</p>	Relevant physical characteristics will be provided in the specification for identity purposes. Physical characteristics are generally irrelevant to defining the general properties of a starting material
	1852-1853	<p>Revise this sentence as follows:</p> <p><i>When relevant</i>, tests to confirm the presence of a counter ion (e.g., sodium, chloride) should be included in addition to other identity tests.</p>	This test should not be considered a general requirement.
	1859-1863	<p>Revise as follows:</p> <p>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).</p>	Consistency with ICH Q3A/B

<b>Section</b>	<b>Guidance Line</b>	<b>Comment</b>	<b>Rationale</b>
Post-Approval Issues	1974-1988 2097-2106	Remove these paragraphs	Post-approval issues are not appropriate for this guidance. Much of this information is GMP related as well.
Glossary	2122	The definition of critical should be revised as follows. ...that must be <i>tightly</i> controlled within predetermined criteria...	A process variable is critical only if it is known to affect drug substance quality <u>and</u> if control of this variable within the proven acceptable range is technically difficult with respect to standard manufacturing experience.
	2157	Add the following definition for interim acceptance criteria Acceptance criteria proposed at time of submission with a proposal for reevaluation as more data is available.	Clarification
	2231-2232	Specification sheet should be defined separately.	Clarification
	2240	Add the following definition for sunset test A test that may be dropped from the drug substance specification after an agreed number of production batches have met certain criteria.	Clarification