



## ABBOTT LABORATORIES Global Pharmaceutical Regulatory Affairs

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

**Re: Docket No. 2003D-0571, CDER 200389. Drug Substance: Chemistry,  
Manufacturing, and Controls Information**

Abbott Laboratories (Abbott) is pleased to have the opportunity to comment on the Draft Guidance for *Drug Substance: Chemistry, Manufacturing, and Controls Information* published in the Federal Register on January 7<sup>th</sup>, 2004.

We commend the Agency on their efforts to maintain drug safety and efficacy throughout the course of a drug's life. However, Abbott believes that dialogue with stakeholders and the practicality of implementing certain requirements described in the draft guidance should be taken into consideration before the draft guidance is finalized, so as to achieve the best results for an effective approach to serve the public health.

Abbott endorses the Pharmaceutical Research and Manufacturers of America's (PhRMA) response to the Agency on this draft guidance, and thanks the Agency for their consideration of our attached comments. Should you have any questions, please contact Richard Poska at (847) 938-5901 or by FAX at (847) 938-3346.

Sincerely,

Richard Poska, R.Ph.

2003D-0571

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**Comments on the  
Draft Guidance to Industry for  
Drug Substance:  
Chemistry, Manufacturing, and Controls Information**

**Docket No. 2003D-0571**

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The following comments on the Draft Guidance for *Drug Substance: Chemistry, Manufacturing, and Controls Information* are provided on behalf of Abbott Laboratories.

**GENERAL COMMENTS**

Abbott shares the FDA's objective to ensure continued drug quality by providing prudent information on drug substance, in the format outlined by the ICH Common Technical Document format. However, Abbott is concerned that the proposed reporting requirements are more complex and time consuming, without appearing to improve drug substance quality. Major areas of concern for Abbott include the determination of starting materials, the identification of critical vs. non-critical parameters, and the definition for terms contained in the glossary. These proposed approaches for drug substance information appear to contradict other FDA "science-based" and "risk-based" approaches to regulatory compliance.

Starting material criteria are particularly concerning, since Abbott does not necessarily believe the criteria proposed achieve the objective of ensuring the quality of the drug substance on an on-going basis. However, it is Abbott's belief that specifications and methods for starting materials can be developed that are sufficiently robust to insure that changes made in the vendor process will have little or no impact on the final quality of the drug substance. The flexibility to allow improved manufacturability does not directly correlate with decrease in quality of the drug substance. It is also Abbott's suggestion that Attachment 1 be completely revised since, as currently written, it does not appear to represent the application of effective risk- or science-based principles.

Throughout the draft guidance, the concepts for non-critical and critical parameters are not clearly defined. Abbott recommends that process control information be limited to those process controls identified as critical. Submission of non critical process controls, adds no value to the submission and provides little advantage to the reviewer. Similarly, Abbott recommends the submission of detailed information in other areas (e.g. type of equipment, quantities of solvents, reagents and auxiliary materials) be limited to critical information, which assures the drug substance meets its specification. Abbott supports a joint FDA/Industry workshop to explore the concepts of critical and non-critical.

**Docket No. 2003D-0571**

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Abbott appreciates the Agency's inclusion of a glossary into the drug substance guidance. However, some terms in the glossary, e.g. critical and post-synthesis materials, need to be better developed, so they do not leave any room for interpretation. Also, there are some terms, e.g. reprocessing, rework, recycling, regeneration, and salvage, which the Agency does not address in the glossary; Abbott feels it would be very beneficial to have a common understanding and approach to these terms.

**SPECIFIC COMMENTS**

Please refer to the attached matrix for specific comments

**Abbott Comments on:  
Draft FDA Guidance "Drug Substance – CMC Information"  
(Docket No. 2003D-0571)  
December 2003**

Line Number	Draft Guidance Section	Comment	Rationale
General	IV.B.2	Limit the narrative in Section 2.2 to critical process controls with their respective ranges; non-critical process controls can be listed (without ranges) in Section 2.4.	"All" process control is too broad a term. Critical process controls, by definition, are all that should be required in section 2.2
General		"Manufacturing Step" as a term is used in different ways throughout the document (pg 11 and 16). Suggested definitions: > Stage (Starting material to first isolated intermediate) > Unit Operations (reaction, isolation) > Manufacturing Steps (heat, cool, charge)	Clarify the use of terms; manufacturing step, reaction step and unit operation.
General		The document states that it will not provide specific guidance on biological or fermentation, there are repeated references throughout the document to these areas. These references should be removed	This guidance should focus on the defined scope and separate guidance should focus on fermentation and biological to avoid confusion
multiple		All references to drug substance (including in the glossary) should be replaced with active pharmaceutical ingredient.	Consistency with current industry practice
52	Introduction	Bullet 4 should be included in the text instead of the list	Does not describe a "type of drug substance" rather it is a type of manufacturing process
59		Peptide bullet should be modified	Synthetic peptides should be included in the scope of this guidance since they are produced using classical small molecule chemistry.
248		product, such as solid state form	particle size distribution is not an inherent physical property
281	II	Regional information: Comparability protocols can be included in both the MF and application. A methods validation package can be included in the application or the MF or both.	
363-365	II.C.	Detailed information on the characterization----of these and other physical forms should be provided	
371-373	IV	Add: A letter of authorization to the drug substance manufacturer's DMF may replace some parts of this section.	
382	IV	The addresses should be for the location where the relevant manufacturing or testing operation will be performed. Addresses for corporate headquarters or offices need not be provided.	Building numbers should be required only for sterile/aseptic operations. According to Changes to an Approved NDA or ANDA, moving between buildings within a site does not have to be reported except for sterile/aseptic processing of sterile drug substances
392	IV.A	The statement should read "Facilities should be ready for inspection when the application is accepted for submission the FDA, or FDA should be notified when a facility will be ready for inspection."	FDA PAI's do not typically occur before formal acceptance of the filing; current forms allow specifying of inspection -ready dates

Line Number	Draft Guidance Section	Comment	Rationale
399	IV.B	Suggested revision: "A flow diagram and a complete description of the processes and critical process controls..."	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with limited added value. Many process controls affect primarily safety, environmental, or business purposes and do not affect quality. Filing should be limited to quality related information.
402, 2115	IV.B (S2.2)	Alternative process: glossary definition requires revision	Definition of alternate process should be made more specific; examples would be helpful in clarifying the intent of the definition
411 -427	IV.B.1	The flow diagram should provide a summary description of the process, strike lines 414-417, 426, & 427	The content of the Flow Diagram should be sufficient to give the Agency reviewer an overall view of the processing to be conducted and the chemistry. Other information is better reserved for the narrative description where the applicant can provide the necessary detail regarding critical operations, critical control parameters and the manner in which they are monitored and controlled in the processing
431	IV.B.1	Flow Diagram: Strike line 431,	Reaction yield is more appropriately discussed in the process development (2.6) section.
440	IV B2	A narrative description of the manufacturing process that represents the sequence of manufacturing steps undertaken should be provided	Changes to the manufacturing batch size need not be reported per current guidance; thus this information should not be required in the application.
443	IV.B.2	The description should identify critical process controls and the associated numeric ranges, limits, or acceptance criteria.	Only critical process controls should be provided in section 2.2. Information on non-critical process controls, as a review aid, can be provided in section 2.6 or in a regional sections, as, for example, a manufacturing example
450	IV.B.2	Starting materials or intermediates used in each step, with chemical or biological names and quantities or molar ratios specified if critical	Absolute quantities do not necessarily add value. Molar ratios are often more meaningful.
452	IV.B.2	Solvents, reagents, and auxiliary materials used in each step, with chemical or biological names and quantities specified only when critical	See rationale for line 450.
454	IV.B.2	Type of equipment used, including materials of construction) if critical for control of material quality	To specify equipment not critical to the control of quality, would add no value to the submission but would increase the size of the document and add burden to industry and reviewers. Additionally most changes to equipment occur post approval are not reportable thus detailing them in the original submission does not add value
457	IV.B.2	Critical process controls and their associated numeric ranges, limits, or acceptance criteria	It should only be necessary to include critical process controls in the application; tests used only for process information, troubleshooting, economic reasons, environmental reasons, etc, and not needed to control quality should not be required.

Line Number	Draft Guidance Section	Comment	Rationale
466-467	IV.B.2	Identification of manufacturing steps that use recycled solvents or auxiliary materials.	Recycled solvents/reagents are those reused in the process without purification. Therefore, designating where recycled materials are used is appropriate. Recovered solvents/reagents are purified such that they meet the same specifications as for new materials as described in Section S.2.3, Control of Materials. Therefore, distinguishing the place where these materials are used is unnecessary
472	IV.B.2	Suggest the following revision: "Yield ranges (weight and/or percent for each manufacturing step resulting in an isolated intermediate or the final API. Typical yields are provided for information only, and are not considered registered parameters; explained deviations from the typical yields would generally need not be considered to be operating outside the registered process	The yields for individual chemical and/or process steps are often not critical quality-indicating parameters, and may be impacted by a number of external parameters. If yields are requested for informational purposes, it should be clear that deviations from the yield generally need not be considered a regulatory deviation.
486 - 494	IV.B.2	The section creates new submission requirements. A risk analysis should be provided that if bovine-derived materials from bovine spongiform encephalopathy (BSE) countries...are used or manipulated in the same facility	Identification of the use of BSE/TSE materials can be accomplished in section 2.3. Potential cross-contamination is better controlled through GMP and should not be a submission requirement  Use of such materials in the same facility depends on various factors (as part of the risk analysis) like the source and kind of material, facility design, equipment, removal/inactivation steps, cleaning, cleaning validation data, etc.
502-506	IV.B.2	Change Process Controls to Critical Process Controls	The definition provided actually describes a critical process control, a non-critical control is one that does not directly affect the quality (specifications) of an isolated intermediate or the API
508-517	IV.B.2	Each of the bullets should be updated to reflect the need for only those operating parameters , environmental controls, process tests and in-process tests which are critical to ensure intermediate or API quality	This request is consistent with the theme that the manufacturing process description should reflect only critical information
538	IV.B.2	The critical operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified either in the flow diagram or the description of the manufacturing process in this section of the application (S.2.2) and in S.2.4.	Minimize duplication of information

Line Number	Draft Guidance Section	Comment	Rationale
541	IV.B.2	Replace with: Tests on intermediates required to ensure the quality of the final drug substance	Only those tests and controls which have been shown to be critical should be included.
550	IV.B.3	The terms "reprocessing", "rework", "recycling", "regeneration" and "salvage" should be included in the Glossary.	The definition should be consistent with those already agreed to in Q7a
577/605	IV	Introducing unrelated material back into the process - ICH Q7A 14.22 - should be included here. In addition, it should be stated that nonchemical enabling steps which are necessary to reintroduce the material into the established process, such as dissolving it in the original solvent, or filtration to eliminate unwanted solid materials, are allowed. Included should be salt making and breaking in order to reintroduce the material back into the process.	These operations do not introduce new chemical steps or reagents to the operations and are low risk.
622	IV.B.3	The use of recycling of filtrates (mother liquors) to recover reactants, intermediates, or drug substances	If recovered solvents are returned to virgin condition, no reporting should be required
628-637		Replace the entire paragraph with "The use of recovered solvents/reagents, including the point at which they might be used in the process, should be included in the description of the manufacturing process. The use of recovered solvents that meet the specifications described in Section S.2.3 need not be described in Section S.2.2. Solvents recovered from other sources (or processes) should be specified in S.2.3. Include definitions for recycled and recovered solvents in the glossary.	As noted above, recycled solvents/reagents are those reused in the process without purification. Therefore, designating where recycled materials are used is appropriate. Recovered solvents/reagents are purified such that they meet the same specifications as for new materials as described in S.2.3. Therefore distinguishing the place where these materials are used is unnecessary.
647	IV.B.3.d.	The regeneration of materials such as column resins and catalysts should be described in S.2.2. if these operations are critical. The critical process controls for regeneration operations should be provided.	The process controls for column, resin or catalyst regeneration improve operational efficiency but are not always critical.
687	IV.C.1	In general, the starting material for filing purposes and the Api starting material as defined by Q7A are the same for a synthetic drug substance	There is no need for different wording from Q7A
697	IV.C.1	Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute a major structural element to the structure of the drug substance	Differentiates it from a reagent, which contributes a minor structural element (line 1671).
698	IV.C.1	A proposed starting material for a synthetic drug substance should be chosen so that sufficient information will be available to FDA on the Drug Substance manufacturing process to evaluate its' safety and quality.	To avoid confusion that the FDA is requesting information on the starting material manufacturing process
704	IV.C.1	The reference to semisynthetic processes should explicitly exclude fermentation derived materials.	Fermentation-derived materials are not covered in this guidance.
712	IV.C.1	(Strike second bullet)	If this is the flow diagram of the full synthesis it is already provided in Section S.2.2, and does not need to be repeated in this section. Information about the proposed starting material synthesis should be required only as necessary to defend the starting material specifications and analytical methods.

Line Number	Draft Guidance Section	Comment	Rationale
769-777	IV.D.	In this section of the application, all critical operating parameters, and process tests should be provided. In addition, critical tests performed on intermediates, through to final drug substance for the purpose of determining suitability for downstream processing should be provided. Their associated numeric ranges, limits or acceptance criteria should be identified. Strike the last two sentences (lines 772 -777)	Discussion of tests should be separated from the discussion of operating parameters. It should not be necessary to provide both critical and non-critical testing done on intermediates, etc if it is not required for APIs
779-782	IV.D.	<p>For all these critical process controls, the associated numeric ranges, limits, or acceptance criteria should be justified. Justification may be based upon scientific judgment and experience gained during the development of the manufacturing process. Summarized information should be provided. Additional information should be provided in this section under the following circumstances.</p> <p>Add: Justification may be based upon scientific judgment, historical data or laboratory scale data should be provided. Summarized information should be provided.</p> <p>A justification summary should be provided. Justifications may be based upon ....laboratory, pilot plant or manufacturing scale data...</p>	<p>Intent of line 780 not clear, "tests" have already been defined as a subset of process controls.</p> <p>"All" experimental data is too broad a requirement. The sponsor should determine how much data is required to support the justification.</p> <p>Strike environmental controls from the glossary.</p> <p>The fill data to support the process controls is available for review during the preapproval inspection.</p> <p>Section 4.4 requires that data from all lots of API (tox, phase I clinical etc). Due to changes in the process it is likely that process control information from those batches will not be relevant to the justification of the commercial process.</p>
807		When the same analytical procedure is used for both the in-process test and the drug substance test, the acceptance criteria for the in-process test should be demonstrated to be appropriate such that the drug substance will meet its acceptance criterion.	It is not appropriate to expect that all in-process tests used in this fashion would have to have specifications that are equal to or tighter than the API specs, an example would be pool criteria for a distillation or a chromatographic separation.
815		When warranted, a specification should be provided for an isolated intermediate to ensure that it has appropriate quality attributes (e.g., LOD or assay or color or purity,...) for further downstream processing. A specification for an intermediate should usually include testing for impurities	Very often the assay is a very gross and ineffective tool for determining the acceptable quality of intermediates. A more effective way of controlling quality is to focus on specific/total impurities.
839-864		Delete sections on photosynthesis materials and unfinished drug substance	Rewording in the beginning of section S.2.4 now incorporates these materials
877		Footnote 15 The appropriate parts of all manufacturing processes should be validated as defined in ICHQ7A. However, in most cases, the validation information is reviewed during facility audits.	It is currently not required to validate all parts of manufacturing processes.
959	V	Remove the phrase "particle size analysis"	Particle size is not an inherent property of the drug substance. Particle size analysis is more appropriately addressed, when necessary, as part of the drug substance justification of specifications
1021-1022	V	Impurities that were once present in the clinical drug substance but that have been....	The discussion should be limited to those that are relevant to the discussion of safety

Line Number	Draft Guidance Section	Comment	Rationale
1049		The following may be required to support the identification of impurities	This level of information for all actual and potential impurities is not warranted.
1063-1065		The qualified level of the impurity, if appropriate, with a cross-reference ....	This section is most efficiently organized as a table of impurities with appropriate information about each. For those that have been qualified in toxicology studies a reference to the appropriate section should be sufficient.
1085	V.I.A	When warranted, a specification should be provided for unfinished drug substance if the drug substance is further processed (e.g., micronized) before it is used to manufacture the drug product, This specification should be included in section 2.4	A specification for unfinished drug substance should not be a constant requirement, only when appropriate
1105, 1115, 2228, 2231/2232		The specification should list....	ICH Q6a & b definition of "Specification" matches the specification sheet as defined in this guidance. FDA should adopt ICH term.
1129	V.I.A	Table 1: Remove the requirement to include the Brand for particle size analyzers Add Footnote: This is an example specification and is not intended to imply that these are typical tests and acceptance criteria for synthesized drug substances	Equipment brands should not be included in the filing, it may be more appropriate to list operating principle  Comparable to footnote in Table 2
1193	V.I.B	Recommendations on the content and format of analytical procedures submitted can be found in ICH Q2A	The is an ICH guidance on this subject. Why reference an FDA guidance that is not yet started?
1229-1230	V.I.C	This information should be provided for the appropriate analytical procedures listed in the specification	Compendia or certain limit of identity tests should not require presentation of validation data. Per USP <1225>
1225	V.I.D	Batch analysis data may be presented either as individual batch analysis reports or as collated batch analysis tables. The batch analysis data should included a description of the batches. This information can be presented (1) with the batch data as space permits or (2) in a separate table with only the batch identity being included with the batch data.	Table presentation of data may be more useful and submission of both individual reports and tabular data is redundant with little if any added value.
1262-1264	V.I.D	The batch analysis reports should include results from the tests that are part of the proposed specification, and those results necessary to support the justification of drug substance specification	All test results for all lots is too inclusive. Testing requirements evolve as the process is developed. Tests may be added or deleted and it may not be appropriate or necessary to collect all data on every lot
1372-1373	V.I.E	Acceptance criteria, for residual solvents should generally be based upon safety, manufacturing capability and analytical variability	Acceptance criteria for drug substance should take into account all three factors regardless of the attribute. Additionally, at the time of submission it is often the case that little manufacturing experience is available.
1396	V.II.S	When the drug substance reference standard is not from an official source, it should be fully appropriately characterized (see section S.3.1 Elucidation of Structure and Other Characteristics).	Change "fully" to "appropriately" because some attributes, such as particle size characterization, do not add value to the characterization of a reference standard
1401-1402	V.II.S	A list of impurity reference standards that are referenced in drug substance analytical procedures should be included in S5	Information should only be required in the application for reference standards which are needed to perform testing specified in the application

Line Number	Draft Guidance Section	Comment	Rationale
1409-1411	VIII	A description of the container closure system for the drug substance should be provided, including the identity of materials of construction of each primary packaging component and its specification, where appropriate (e.g., when a unique or non-standard material as used in the container closure system)	The request to provide specifications for commonly used packaging component (e.g. HDPE or LDPE bags) is considered unnecessary. It should continue to be sufficient to simply state the material of composition for most container closure systems, unless a unique system is required.
1414-1417		The suitability of the container closure system should be discussed with respect to, compatibility and safety of the primary package component'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.	Consistency with the FDA guidance; Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)
1437	IX.B	A postapproval stability commitment should be provided	Stability protocol is available during GMP inspection, make reference to Q1A
1465	IX.C.1	A summary of changes in analytical procedures that affect the reported results) should be provided if the analytical procedure was changed over the course of generating the stability data...	Not all analytical changes need to be discussed; some are very minor
1490-1495	IX.C	Results from drug substance stress testing should be provided in this section or referenced from other sections	"Any" is too broad and should be deleted. Results should be provided for the stress studies as described in ICH Q1A (R2)
1628	XI.A	Executed Batch Records	Both production and batch record terms are used, standardize on a single term for clarity
1588	X.B	Certifications and/or documentation relating to the safe use of bovine-derived materials should be provided, as appropriate. Current requirements include certification that bovine-derived materials are not sourced from BSE countries as defined by the U>S> Department of Agriculture	Since the requirements are expected to change continually in this issue, guidance here should be kept general and cross-reference up-to-date and specific requirements provided elsewhere
2122	Glossary	Describes a process step or process control (.....) that must be controlled within predetermined criteria to ensure that the drug substance meets it's specifications. Factors that may be considered: Impurities are either produced or removed that are not later removed in the process and/or the physical properties of the API are controlled. Additionally the sensitivity of the API quality to changes in the parameter and level of process control of the parameter are evaluated.	Additional guidance is needed to in order to generate a more consistent definition which also offers the opportunity to incorporate the principle of risk-base analysis into the definition. A process variable (parameter) is critical only if it is known to affect drug substance quality and if control of this variable within the proven acceptable range is technically difficult with respect to standard manufacturing experience.
2184-2191		Revise definition of post-synthesis materials to remove those materials that are already covered as "non-isolated intermediates" under the existing intermediate definition	Definition of post-synthesis material and intermediate are contradictory, if a post-synthesis material is post final intermediate and "undergoes further molecular change before it becomes the drug substance" it most certainly is a non-isolated intermediate.