



Connecting People, Science and Regulation®

PDA Global Headquarters

Bethesda Towers
4350 East West Highway
Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296

www.pda.org

OFFICERS

Chair:
Maik Jornitz
Sartorius Stedim Biotech

Chair-Elect:
Anders Vinther, PhD
Genentech

Secretary:
Rebecca Devine, PhD
Regulatory Consultant

Treasurer:
Harold Baseman
ValSource

Immediate Past Chair:
John Shabushnig, PhD
Pfizer

President:
Richard M. Johnson

DIRECTORS

Jette Christensen
Novo Nordisk

Gabriele Gori
Novartis Vaccines and Diagnostics

Zena Kaufman
Abbott

Steven Mendivil
Amgen

Michael Sadowski
Baxter Healthcare

Junko Sasaki
Dainippon Sumitomo

Sue Schniepp
OSO BioPharmaceuticals

Amy Scott-Billman
GlaxoSmithKline

Lisa Skeens, PhD
Baxter Healthcare Corporation

Christopher Smalley, PhD
Merck & Co.

Martin VanTrieste
Amgen

Glenn Wright
Eli Lilly

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

RE: Draft Guidance entitled "Q11 Development and Manufacture of Drug Substances"; Docket No. FDA-2011-D-0436

Dear Sir/Madam:

PDA is pleased to offer comments on the ICH draft guidance entitled "Q11 Development and Manufacture of Drug Substances". PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in drug substance and drug product development, CMC and GMP regulations, including members representing our Biotechnology, Regulatory Affairs and Quality, and Science Advisory Boards. PDA appreciates the opportunity to offer comments and wishes to thank FDA for the opportunity to do so. These same comments are also being submitted to the European Medicines Agency as part of their consultation process.

PDA commends this continuing initiative to develop global consensus guidance. In General, we find this guidance an impressive effort to capture the latest thinking around modern pharmaceutical quality and development science. We are especially pleased to note the guidance's emphasis on design space, risk management and the use of a Quality by Design approach.

Enhanced approach: The guidance makes frequent references to what is described as "the enhanced approach". Since there is no consensus in the industry over what this really means, it would be helpful if the term were defined in the Glossary or a reference for the definition were provided. It appears the enhanced approach referred to is the same as (or very much aligned with) the Quality by Design concept discussed in Q8 and referred to in the documents supporting the implementation of Q8/Q9/Q10 and the ICH Quality IWG Points to Consider Guide for ICH Q8/Q9/Q10 Guidelines. The connections between these terms and concepts should be explicit.

United States Food and Drug Administration
September 1, 2011

In addition, our reviewers found the dual focus on both the traditional and enhanced approaches to development, as presented in the draft guidance, somewhat confusing. We recognize the need to provide a continuum of approaches, as allowed by regulations and historical precedent, as appropriate for each case and company business decision. However, it might have been preferable to acknowledge that the two approaches are not mutually exclusive and that either approach or a combination could be used (as described in the concluding paragraph of the Introduction section) and then focus on providing guidance on the execution of the enhanced approach only. Perhaps an acceptable solution would be to refer to existing guidelines that address the traditional approaches and use Q11 to promote and describe only the “enhanced” approach.

Existing ICH guidance: There are several areas where Q11 adds language that is already contained in existing ICH guidance. Q11 could be made briefer by just making reference to these guidances rather than re-stating them. This would also avoid divergent or conflicting interpretations by users of the various guidelines.

Large molecule/small molecule guidance: Our commenting team did feel that splitting the guidance into two sections, one addressing large molecules and the other small molecules, would have added greater clarity. We recognize this approach may be outside the remit of the Expert Working Group who developed the guidance, but we raise this point for your awareness.

We would be pleased to offer our expertise in a meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President, PDA

CC: Robert L. Dana, PDA
Rich V. Levy, PhD, PDA
James Lyda, PDA

**PDA Comments – FDA Draft Guidance Entitled,
“Q11 Development and Manufacture of Drug Substances” (Docket No. FDA-2011-D-0436)**

PDA No.	Line No.	Current Text	Proposed Change	Rationale
1	NA	NA	It is important that Q11 not conflict with Q7. There should be no redundancies, differences, or ambiguities.	It is desirable to keep regulatory guidance as transparent as possible and having two API guides is more cumbersome than having one.
2	76 - 80	In an enhanced approach, risk management ... for evaluation in further studies to establish any design space(s) and control strategies applicable over the lifecycle studies to establish <i>any design space(s) and</i> control strategies (optionally including a design space) applicable over the lifecycle ...	Align with the wording in Q8 R2
3	82	As discussed in ICH Q8, ... can create the basis for more flexible regulatory approaches.	As discussed in ICH Q8, ...can create the basis for more flexible regulatory <i>and manufacturing</i> approaches. The degree of regulatory and <i>manufacturing</i> flexibility is ...	Benefits of the enhanced approach should accrue for both regulators and manufacturers.
4	87	A company can use ... or a combination of both.	A company can use ... or a combination of both. <i>For example, even when an enhanced approach is used for development, a traditional approach for the control strategy is acceptable</i>	Coupling a traditional approach to control strategy with an enhanced approach to development is important and should be included in the introduction.
5	100	The goal of manufacturing process development for the drug substance is to establish ...	The goal of manufacturing process development for the drug substance is to establish ...	Redundant wording.

**PDA Comments – FDA Draft Guidance Entitled,
“Q11 Development and Manufacture of Drug Substances” (Docket No. FDA-2011-D-0436)**

PDA No.	Line No.	Current Text	Proposed Change	Rationale
6	107	The intended quality ... which can influence the development of the drug product	The intended quality ... which can influence the development <i>and performance</i> of the drug product	More complete description of drug substance process development objectives.
7	116	Quality Risk Management ... and increasing the assurance of routinely achieving ...	Quality Risk Management ... and increasing the assurance of <i>routinely</i> achieving ...	Editorial change
8	151	Determining the functional relationships that link material attributes and ...	Determining the <i>functional</i> relationships that link material attributes and ...	The term “functional” may limit the type of relationships that need to be considered and is not necessary.
9	187 - 189	Prior knowledge can be used at the beginning of development and assessments can be iteratively updated with development data (including data from non-clinical and clinical studies) during the lifecycle.	Prior knowledge can be used at the beginning of development, <i>and anytime thereafter</i> , and assessments can be iteratively updated with development data (including data from non-clinical and clinical studies) during the lifecycle.	The value of prior knowledge is not limited to the beginning of development. This is contradictory to the lifecycle model
10	348 - 351	To facilitate the approval of a design space for a complex product, such as a biotechnological/biological product, an applicant can choose to provide information on how movements within the design space will be managed post approval. This could help the reviewer understand how residual risk will be managed.	The Glossary should provide additional clarification of what a “complex product” is, especially vis a vis chemical drugs.	This term is unclear and may lead to inconsistent interpretation of the guideline.

**PDA Comments – FDA Draft Guidance Entitled,
“Q11 Development and Manufacture of Drug Substances” (Docket No. FDA-2011-D-0436)**

PDA No.	Line No.	Current Text	Proposed Change	Rationale
11	368 - 371	The physical properties of a drug substance are determined ... at the end of the manufacturing process.	<i>For example</i> , the physical properties of a <i>synthetic</i> drug substance <i>may be</i> determined ...	Not all drug substances are solids or can be handled as solids. Removal of impurities can be and is achieved in many different ways. It depends on the synthesis whether the physical properties are determined during the final step or not.
12	399 - 402	A starting material is incorporated as a significant structural fragment into the structure of the drug substance. “Significant structural fragment” in this context ...	“A starting material is incorporated as a significant structural fragment into the structure of the drug substance (<i>as described in Q7</i>). “Significant structural fragment” in this context ...”	Q11 has placed emphasis on the term by adding quotations around the phrase. This phrase is already found in Q7 in the definition of API starting material and the text of Q11 should indicate such.
13	449 - 453	In some instances, ... manufacturing process. Specifications should normally ... purified starting material.	Delete this entire paragraph.	This is all described in ICH Q7 and is unnecessarily duplicated in Q11.
14	658 - 659	The knowledge and process understanding should be shared across all sites involved in manufacturing the drug substance.	Change to read, “The knowledge and process understanding should be shared across all sites involved in manufacturing the drug substance (ICH Q10 1.6.1) . <i>as needed to perform the manufacturing process and implement the control strategy across sites involved in manufacturing the drug substance.</i> ”	As written, the text could be taken to mean that all development information would need to be shared with a contract manufacturer. The recommended revision would limit the scope of shared information to only that needed to effectively perform manufacturing operations pertinent to that site.

**PDA Comments – FDA Draft Guidance Entitled,
“Q11 Development and Manufacture of Drug Substances” (Docket No. FDA-2011-D-0436)**

PDA No.	Line No.	Current Text	Proposed Change	Rationale
15	675 - 869	Illustrative Examples	None	The examples at the end of the draft guidance generally add clarity and are desirable
16	870 - 912	Glossary	None	The use of a Glossary lends clarity to terms used in the draft guidance and is desirable.