



01 September 2011

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

Submission of comments on: [Docket No. FDA-2011-D-0436]; International Conference on  
Harmonisation; Draft Guidance on Q11 Development and Manufacture of Drug Substances

ISPE is pleased to have the opportunity to provide comments to FDA and EMA on the above guidance. The draft guideline, whose publication is warmly welcomed, provides a wealth of helpful information to the developers of both chemical and biotechnology drug substances. However, two major new concepts are introduced which increase the regulatory expectations from those introduced in Q8 (R2). As you will note from our comments, we would propose significant redrafting to clearly explain design space movement and its implications to the control strategy and quality system. In addition, a new tier of criticality has been introduced through Example 2, which implies 3 categories of process parameters, but this is at risk of causing confusion about what might be included in a design space. We would also propose that Example 2 be redrafted.

Please feel free to contact me should you have any questions.

Best Regards,

A handwritten signature in black ink that reads 'Robert P. Best'.

Robert P. Best  
President/CEO ISPE



## ISPE Regulatory Comment Form

**Proposed Regulation/Guidance Document:** ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities)

**Due Date for Comments:** 01 September 2011

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No.	LINE NUMBER	PROPOSED CHANGE	RATIONALE
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The draft guideline, whose publication is warmly welcomed, provides a wealth of helpful information to the developers of both chemical and biotechnology drug substances. However, two major new concepts are introduced which increase the regulatory expectations from those introduced in Q8(R2).

Firstly, the suggestion that an applicant can ‘choose to provide information on how movements within the design space will be managed post approval’. A key concept of Q8(R2) is that movement within a design space is not a change and that no regulatory action is required for such movement. The Q11 draft is, by implication, expecting that an applicant with a ‘complex’ (undefined) product submit a protocol for managing design space movement and that this will need to be pre-approved by the regulators. This detracts from the flexibility (and applicant responsibility) anticipated by the use of a design space and means that any movement is now subject to a regulatory action, even if this is now to be concluded prior to approval. If this is indeed the case, and an applicant who chooses not to submit a protocol will find themselves at risk of being denied approval, then the guideline should explicitly state this and full opportunity given to discuss the implications. Note that such an expectation is not included in Q8(R2), leading to a significant lack of consistency. Significant redrafting may be needed to explain clearly this need and its implications to the control strategy and quality system.

Secondly, a new tier of criticality has been introduced through Example 2, which implies 3 categories of process parameter, but this is at risk of causing confusion about what might be included in a design space. A process parameter included in a design space generally triggers a regulatory action if a range change is proposed. Parameters A-F were considered high risk, (and should be recognised and categorised as CPPs), and were included in a design space. However, it is entirely conceivable that only a sub-set of these CPPs might have been included in a design space. Can a proposal for changes to CPPs be submitted if these are not part of a design space?

Creating a middle tier of risk (aka criticality) creates further confusion. Isn't this just another name for what many had proposed earlier to be ‘Key Parameters’, a proposal which was rejected? G, H and I are not CPPs, and (in this example) were not included in a design space although they could have been. But now Example 2 implies that the applicant will need to satisfy the regulators on two aspects. Firstly that there are procedures in place to assess and manage the residual risks associated with change of parameters that were not CPPs but perhaps might become CPPs if their ranges are extended, presumably by submission of a post-approval change protocol, and secondly that there is a commitment to further study these parameters in order to ‘assure continual improvement’. The prospect of having this intermediate but rather arbitrary category for drug substances but not drug products is also inconsistent and should be avoided. Example 2 should be redrafted.

1.	70	...as they pertain to the development and manufacture of drug substance and, in particular, to the generation, fate and purge of impurities	The introduction should include reference to the unique aspect of drug substance manufacture in which impurities are generated, transformed and purged during processing. Note title of Q11 uses ‘system’ (singular).
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2.	116	...and increasing the assurance of routinely producing batches of the desired quality.	Why focus on 'results'? The objective should be to product batches of the desired quality.
3.	127		ISPE commends the recognition of "prior knowledge, including platform manufacturing" as process development tools.
4.	220	delete 'potential': this would be consistent also with the construction of Q8(R2).	While CQAs may be 'potential' in the very early stages of development, in this section the guideline is discussing linking material attributes and CPPs to the CQAs identified in 3.1.4, and not to potential CQAs.
5.	229	Design and conduct <del>experiments and/or mechanistic</del> studies (e.g., <b>mechanistic and/or kinetic evaluations</b> , multivariate...	Mechanistic studies are a subset of experiments- initial phrasing is inaccurate.
6.	232	Analyse and assess the data.....	Previous bullets use the imperative form of verbs
7.	235-239		ISPE commends the recognition of small scale models and their extrapolation across scale and equipment.

8.	241-245	<p>Add new paragraphs, as follows:</p> <p>Design space is generally determined during product development through an iterative process. Initially, the links of the drug substance and formulation processes to the QTPP may be tenuous, as central elements of safety margins, clinical dose range, and the like are becoming understood in parallel with the early conceptualization and development of the process. It is not unreasonable, therefore, to take a phased approach, taking advantage of new safety and clinical information to enhance the strength of process-product linkages over time.</p> <p>Design space may be based on prior knowledge, and/or be based on first principles or empirical understanding of the process. Qualitative and quantitative models can be useful towards demonstrating process understanding.</p> <p>A design space can be determined per unit operation, per cluster of unit operations or for the entire process</p>	<p>The section on design space does not provide significant guidance on how to develop a design space. It merely discusses the desired outcome that a design space provides. The "how" is scattered in various places throughout the document.</p>
9.	248	<p>...using prior knowledge the commercial manufacturing should be appropriately validated...</p>	<p>Validation should be associated with the commercial manufacturing process.</p>

10.	250-257	For chemical entity development, a major focus is control of formation, fate, and purge of impurities through every step of a manufacturing process. It is important to understand the formation, fate (whether the impurity reacts and changes its chemical structure), and purge (whether the impurity is removed via crystallization, extraction, etc.) as well as their relationship to the resulting impurities that end up in the drug substance as CQAs. All steps (or unit operations) should be evaluated to establish their potential to effect impurity levels and to establish appropriate control for impurities as they progress through subsequent process operation(s).	This section on the fate and purge of impurities does not belong in the design space section. It is equally applicable to the traditional approach, hence this section could be more appropriately placed after line 63
11.	259 Also 320	The wording of Q8(R2) Section 2.3 could be used in this section almost verbatim. If this is not deemed acceptable, delete 'important aspects' and change to ....were used to establish the manufacturing process and control strategy.	Section 3.2 describes how the significance of a drug substance change should be assessed but introduces a new concept with no explanation, namely 'important aspects'. What is the definition of an 'important aspect' and where and how would these be listed? In the absence of a definition, this concept should be removed.
12.	298-310	A description and discussion should be provided of significant changes made to the manufacturing process <del>or site of manufacture of</del> for drug substance batches used in support of the marketing application	Site changes are common during development, scale-up and transfer of a process. These site changes are generally reported in the Batch Analysis section of the filing. Hence, site of manufacture need not be included as a significant change that requires discussion in the Process History Section. If this is a differential concern between biologics and synthetic molecules, the language should be amended accordingly.

13.	322	Risk assessments, both formal and informal, should be summarised. Experimental studies should be summarised with a level of detail sufficient to convey an understanding of the purpose of the study, the experimental design or protocol, analysis and data collection, and the conclusions reached. The impact of the study on the development of the manufacturing process should be described.	It is not clear what is expected, but the recommendations appear to be a significant escalation compared to current expectations. Having 'study or risk assessment' in the same sentence confuses the two concepts. There cannot be an 'end use' of a risk assessment. Experimental studies may not result in any drug substance being produced. For example, it is not unusual to carry out multiple robotic procedures and listing all of these would be tedious with no value to the understanding or assessment.
14.	330	The risk assessment study results on which....	No need to specify tools in regard to risk assessment.
15.	331-332	Example 2 shows one possible approach for risk ranking of design space parameters.	Example 2 shows one approach to risk ranking of design space parameters.
16.	333	Where development refers to specific prior knowledge appropriate references (e.g. literature reference) should be provided: where this is not possible, the relevant information should be reproduced, and, where appropriate, .....	"Specific" prior knowledge should not result in data having to be provided. Although it is not clear why the authors choose to refer to 'specific' as opposed to (presumably) non-specific knowledge, literature references can often suffice. In the absence of a literature reference, it would seem better to reproduce that prior knowledge, so that the original context is preserved.
17.	335	Small scale models used to support development of the manufacturing process should be described	The use of small scale models needs to be linked to the development of the commercial manufacturing process

18.	337-338		ISPE commends the recognition that the content in the Description of the Manufacturing Process represents the applicant's commitment for the manufacture of drug substance.
19.	348-351	<p>If a statement is considered necessary to facilitate the approval of a design space for a biotechnological product, then we would recommend deletion of reference to "complex product" and would propose alternative text as follows:</p> <p>"To facilitate the approval of a design space for a biotechnological 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."</p>	This section introduces additional requirements beyond what is described in ICH Q8 and would discourage the filing of an enhanced approach. The statement regarding approval of design space for a complex product is a major concern. It adds an unnecessary constraint on the applicability of design space and raises regulatory expectations, particularly for chemical entities. The proposals are inconsistent with ICH Q (R2)
20.	358		ISPE commends the General Principles section on the selection of regulatory starting materials and that all should be considered in the selection process.
21.	360	All the following general principles should be.....	Indicate that all the principles should be considered aligned with line 290 (EMA), 404 (FDA)
22.	412-415		ISPE commends the clarification provided that an isolated intermediate for a semi-synthetic drug substance can be proposed as a starting material according to the general principles.



23.	431	A commercially available chemical is usually one that is sold as a commodity in a pre-existing <del>non-</del> pharmaceutical market...	Delete "non-pharmaceutical" as some commodity chemicals are used solely in the production of pharmaceuticals.
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24.	518	<p>In either the traditional or enhanced approach, the control strategy can include robust controls designed into the process such that an attribute is assured of being within its appropriate limit, range, or distribution without testing the final drug substance. For example in a synthetic process that uses an organic solvent in an early step, removal of the solvent could be demonstrated at that step and therefore testing for the solvent would not be included in the final drug substance specification. For biotechnology/biological products, testing for adventitious agents is an important in-process control that is normally done in the unprocessed bulk instead of in the final drug substance.</p> <p>In Real-Time Release Testing (RTRT), in-process testing and/or monitoring directly impact the decision for batch release and are performed in lieu of testing on the final drug substance. Use of RTRT should provide no less assurance of conformance to the drug substance specification than if testing on the finished drug substance were performed.</p> <p>For example, when considering the use of RTRT, applicants should determine whether there are any factors downstream from the point at which RTRT will be employed that might impact the quality of the drug substance, such as temperature changes, oxidative conditions, light, ionic content, and shear. For example, when considering the use of RTRT, applicants should determine how factors downstream from the point at which RTRT will be employed impact the quality of the drug substance, such as temperature changes, oxidative conditions, light, ionic content, or shear. Once these factors are understood RTRT specifications can be established that will ensure that the drug substance, if tested, will meet its specification. For a drug substance the RTRT specification does not necessarily need to be identical, or tighter, than the corresponding drug substance specification. Also, when RTRT is proposed for a drug substance CQA, the drug substance specification should include a suitable analytical procedure and associated acceptance criteria to enable independent testing and, if appropriate, stability testing. RTRT can replace release testing on the finished drug substance, but does not replace the review and quality control steps called for under GMP to release the batch.</p>	<p>The document does not provide guidance on real-time release testing and the end of section 6.1.2 would be an appropriate place to introduce the topic with the following suggested text.</p>
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25.	562	There is no requirement to run qualification batches at the outer limit of the design space during process validation studies at commercial scale. The design space should be sufficiently explored earlier during development studies	Introduce a sentence that states that there is not a regulatory expectation that the outer limits of a design space be evaluated during process validation studies at a commercial scale.
26.	563-573		ISPE commends the use of data from small-scale studies to support the overall validation package
27.	635		Generally without a harmonized process for post-approval change, this section provides no incentive for an innovator company to make continual drug substance manufacturing improvements in a global market. The regulatory barriers to change remain high.
28.	638	...promoting continual improvement across the entire product lifecycle coupled with more flexible regulatory approaches.	Reference the concept of more flexible regulatory approaches as introduced in section 1.

29.	663-669	Proposed changes to the manufacturing process must be evaluated for the impact on drug substance critical quality attributes. Evaluation should be as close as possible to the point in the process at which the change is made (i.e. showing equivalence at the compound just after the change). For example, for small molecules equivalence may be judged by comparison of impurity profiles. A compound is considered equivalent if there are no new impurities (at the ICH Q3 qualification level) and no increase in known impurities at the specification level. Additionally the change should not involve a genotoxic impurity. For biotech products the concept of equivalence is replaced by the concept of comparability (see ICH Q5E).	This section should be expanded as proposed below to include the concept of chemical equivalence and comparability to further encourage innovator companies to make process improvements.
30.	670	Movements within the Design Space, which do not require approval by regional regulatory authorities, also should be subject to internal change management processes.	As movement within design space is defined as not being a change (glossary) it is inconsistent to now state that movement is a change. Additionally, 'this' is a pronoun with no prior noun.
31.	739	replace "this Risk" with "a Risk"	Editorial
32.	776	Remove the concept or draft appropriate sections (including glossary and illustrative example(s)).	This figure introduces a new concept of an intermediate category of risk. There is no guidance provided within the main guideline as to how the intermediate category should be identified and documented.
33.	852	Delete 's' in cell "Specs for starting material D)	Editorial: Should be specification (singular) to be consistent with Q6A

34.	854	Delete the second sentence of Footnote 1.	Footnote 1 is an escalation of regulatory requirements, certainly in Europe (see CPMP/QWP/450/03), and is contrary to sound scientific principles. It should be acceptable to validate the purge of the residual solvent (just as it is acceptable to demonstrate the purge of any other organic impurity) and not to have to commit to a periodic evaluation of the manufacturing process.
35.	897	Delete 'by the same applicant'.	The proposed definition of platform manufacturing being something used by the same applicant is unnecessarily restrictive. There are commercial companies offering platform technologies to applicants and their expertise should be equally acceptable.