

**ICH Q8: Pharmaceutical Development - Step 2**  
**Docket No. 2005D-0021**

Line No(s).	Section No. / Item	Statement of Concern(s) with Explanation	Proposed Change
13 -17	1.1 Objective of the Guideline	Reverse the sentences and avoid the comparative when no comparison can be made	The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. This guideline also indicates areas where, based on pharmaceutical and manufacturing sciences, flexible regulatory approaches become possible.
24 - 25	1.2 Background	This document is not being considered based on scientific risk management.	This plan emphasizes an integrated approach to review and inspection taking into account scientific risk management.
42	2. Pharmaceutical Development	The term "reproducible" used here works against the philosophy of the guidance itself. Indeed, this reduces the flexibility that one would acquire when understanding the process and by then applying process controls that would enable the operator to manage efficiently the process variables. The goal is not to work in a "frozen-in-time way" anymore, but to be able to dynamically control the process.	...the manufacturing process should <b>CONSISTENTLY</b> deliver the quality of the product

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68 -70	2. Pharmaceutical Development	The meaning of this paragraph is unclear, i.e., "other pharmaceutical development studies" (=additional studies than usually needed for development?), "wider range of material attributes, processing options and process parameters" (than tested or evaluated during development?).	Please clarify wording or delete this sentence.
81 - 83	2. Pharmaceutical Development	It is suggested to rephrase "...over a range of material attributes..." The idea is to determine which parameters are critical, and then to focus on those in order to be able to control them. The way it is written right now could imply that ALL attributes have to be explored.	"...over a range of <b>critical</b> material attributes ..."
208 - 210	2.2.3 Physicochemical and Biological Properties	Delete robustness of manufacturing process and address it under section 2.3	
218 - 221	2.3 Manufacturing Process Development	The appropriateness of components is confirmed by formulation development.	... to address the selection of the manufacturing process and confirm the manufacturability of the components.
228 - 230	2.3 Manufacturing Process Development	Adapt the sentence to the definition of quality.	An assessment of the ability of the process to reliably produce quality (e.g., the ...) should be provided.
233 - 234	2.3 Manufacturing Process Development	Adapt the sentence to the definition of quality.	... to ensure that quality is produced.

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258 - 260	2.3 Manufacturing Process Development	Process robustness can only be appropriately assessed if all possible changes in the future can already be anticipated and evaluated during development. From a scientific point of view this is highly unlikely.	Please delete this paragraph.
265 –268	2.4 Container Closure System	Risk-based approach should be explicitly mentioned for container closure systems	Consideration should be given to the intended use of the drug product and the likelihood of the drug product – packaging component interaction as well as the suitability of the container...
278 - 279	2.4 Container Closure System	Possible decision Tree similar to <b>2.5. Microbiological Attributes</b> should be mentioned	..., and the safety of materials of construction, (e.g., Decision Tree Appendix III in EMEA <i>Guideline on Plastic Primary Packaging Materials</i> ).
302 - 306	2.5 Microbiological Attributes	Revise wording for clarification.	Antimicrobial preservative effectiveness should be demonstrated during development. The lowest ... effectiveness test. Chemical testing for preservative content should be part of the drug product quality control.
314- 316	2.6 Compatibility	Delete the last sentence because of repetition and cover its content in the first sentence	The compatibility of the drug product with reconstitution diluent(s), mixing compounds or dosage devices (e.g., ...
313 - 314	2.6 Compatibility	The “likely extremes of concentration” cannot be sufficiently anticipated since the reconstitution is usually not performed under controlled conditions.	Please delete “likely extremes of concentration”.

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339 - 340	3. Glossary - Quality	Requirements are either fulfilled or not fulfilled. There is no such thing like a degree of fulfilment. It is also not clear how the quality is defined for a drug product... at a certain time, the FDA was talking about the quality of a drug product as "derived from the clinical studies".	The characteristic by which a product, a system or a process can be distinguished or identified as fulfilling the requirements of a given set of inherent properties (specification)
342-343	3. Glossary - Risk	Help the reader and tell him the kind of combination so he does not have to look into ISO/IEC Guide 51 to understand Q8	The combination, R, of the probability of occurrence of harm, given by the numerical factor P, and the severity of that harm, given by the numerical factor S; therefore $R = P \times S$
additional	3. Glossary	Scientific understanding	Please give a definition of scientific understanding in the glossary (examples)