Q11 DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES

QUESTIONS AND ANSWERS
(regarding the selection and justification of starting materials)

For questions regarding this draft document contact (CDER) Stephen Miller 301-796-1418.

Q11 Implementation Working Group
Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
Questions and Answers
(regarding the selection and justification of starting materials)

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH Secretariat, Chemin des Mines 9, P.O. Box 195, 1211 Geneva 20, Switzerland

Telephone: +41 (22) 338 32 06 - admin@ich.org, http://www.ich.org

In order to facilitate the implementation of the Q11 Guideline, the ICH Q11 Implementation Working Group has developed a series of Q&As

ICHQ11 Q&As
Document History

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References

ICH Q3A Impurities in New Drug Substances (R2) 25 October 2006
ICHQ6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances October 1999
ICHQ6B Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products March 1999
ICH Q7 Good Manufacturing Practice of APIs November 2000
ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Questions and Answers 10 June 2015
ICH Q8(R2) Pharmaceutical Development August 2009 Part I: 'Pharmaceutical Development' November 2006 Part II: 'Annex to Pharmaceutical Development', November 2008
ICH Q9 Quality Risk Management and the ICH Q9 Briefing pack November 2005
ICH Q10 Pharmaceutical Quality Systems June 2008 ICH Q-IWG Training Programme for ICH Q8/Q9/Q10 November 2010
ICH Q11 Development and Manufacturing of Active Pharmaceutical Ingredients May 2012
ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals to Limit Potential Carcinogenic Risk 23 June 2014

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PREFACE

Since the ICH Q11 guideline was finalised, worldwide experience with implementation of the recommendations on the development and manufacture of drug substances has given rise to requests for clarification relating to the selection and justification of starting materials.

This Question and Answer (Q&A) document is intended to provide additional clarification and to promote convergence on the considerations for the selection and justification of starting materials and on the information that should be provided in marketing authorisation applications and/or Master Files. The focus of the Q&A document is on chemical entity drug substances.

The scope of this Q&A document follows that of ICH Q11. ICH Q11 is applicable to drug substances as defined in the Scope sections of ICH guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. ICH Q11 does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in ICH Q11 and this supporting Q&A document are important to consider during the investigational stages.

Generally, it is anticipated that API starting materials that have already been accepted by regulatory authorities (e.g., for use in authorized medicinal products) would not need to be re-justified against the ICH Q11 general principles or the recommendations included in this Q&A document, unless significant changes are made to the manufacturing processes and controls. However, a starting material accepted for one manufacturer's process may not be considered acceptable for a different manufacturer's process, if the proposal does not comply with the guidance in ICH Q11.

“Applicant” is used throughout the Q&A document and should be interpreted broadly to refer to the marketing authorization holder, the filing applicant, the drug product manufacturer, and/or the drug substance manufacturer.

Designation of starting materials should be based on process knowledge for the intended commercial process. **It is emphasized that all of the general principles in ICH Q11 Section 5 should always be considered holistically, together with the clarifications in this Q&A document, rather than applying a single general principle or Q&A clarification in isolation.**

ICHQ11 Questions and Answers

21 **1. INTRODUCTION**

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

22 **2. SCOPE**

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

23 **3. MANUFACTURING PROCESS DEVELOPMENT**

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

24 **4. DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS**

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

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26 **5. SELECTION OF STARTING MATERIALS AND SOURCE MATERIALS**

#	Date of Approval	Questions	Answers
5.1		ICH Q11 states that "*A starting material is incorporated as a significant structural fragment into the structure of the drug substance*." Why then are intermediates used late in the synthesis, which clearly contain *significant structural fragments*, often not acceptable as starting materials?	The selection principle about "*significant structural fragment*" has frequently been misinterpreted as meaning that the proposed starting material should be structurally similar to the drug substance. However, as stated in ICH Q11, the principle is intended to help distinguish between reagents, catalysts, solvents, or other raw materials (which do not contribute a "*significant structural fragment*" to the molecular structure of the drug substance) from materials that do. It is not intended to dictate the selection of either a very early or a very late intermediate as the starting material. A proposed starting material may be several steps from commercially available materials, provided it is not a small number of chemical transformation steps from the drug substance, and provided the justification acceptably addresses the ICH Q11 general principles. The presence of a "*significant structural fragment*" should not be the sole basis for of starting material selection. Starting materials justified solely on the basis that they are a "*significant structural fragment*" probably will not be accepted as starting materials by regulatory authorities, as the other principles for the appropriate selection of a proposed starting material also require consideration.
5.2		ICH Q11 recommends that "*manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in Section 3.2.S.2.2 of the application*." At what level would a related substance or mutagenic impurity be considered to impact the impurity	For non-mutagenic related substances, an impurity that is likely to be present in the drug substance at a level above the ICH Q3A Identification Threshold is considered to have an impact on the impurity profile of the drug substance. A mutagenic impurity that is likely to be present in the drug substance above 30% of the ICH M7 acceptable intake is usually considered to impact the impurity profile of the drug substance. Any of the approaches described in ICH M7 can be used to determine which impurities are likely to be present above the 30% threshold. The 30% threshold serves an analogous function in ICH M7 to the Identification Threshold in ICH Q3A. In line with ICH M7 and ICH S9, there are situations (e.g., when the drug substance is itself genotoxic, and other circumstances as described in these guidelines) when the selection of the starting material for a drug substance does not need to specifically consider the mutagenic impurity profile at the levels described above. In such cases, mutagenic impurities are not considered to

		profile of the drug substance?	impact the impurity profile of the drug substance unless they are above the ICH Q3A Identification Threshold. Impurities that persist through multiple steps of manufacture should be considered in conjunction with Q&A 5.3.
5.3		What is meant by impurities that "*persist*" in ICH Q11 Example 4?	ICH Q11 recommends that "*manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in Section 3.2.S.2.2 of the application.*" However, as described in ICH Q11 Example 4, this principle does not necessarily apply when impurities originate early in the manufacturing process and "*persist*" across multiple steps, provided that the steps prior to the proposed starting material over which the impurities persist do not themselves impact the drug substance impurity profile. In Example 4 there are multiple steps (from Compound B to Compound D) that do not impact the drug substance impurity profile. Without this exception, these steps would have to be included in Section 3.2.S.2.2 of the application. Impurities that persist may or may not react in subsequent steps, but are not removed to the extent that they would no longer be considered to impact the drug substance impurity profile [For "impact" see Q&A 5.2]. For example, an impurity that persists might have physico-chemical properties (e.g., solubility) similar to other intermediates or the drug substance, like the enantiomer in Example 4, which could make its removal intrinsically difficult. ICH Q11 Example 4 illustrates that when the synthetic route contains an impurity that persists, it can be acceptable to control the impurity in the starting material specification even though it impacts the impurity profile of the drug substance. Therefore, it is not always necessary to include steps that form such an impurity in Section 3.2.S.2.2, provided that the other ICH Q11 general principles are addressed [ICH Q11 Section 5.1.1]. Example 4 is not exclusive to stereoisomers and can be applied to other types of impurities that persist. In Example 4 there are 3 chemical transformation steps between the starting material D and the drug substance. The 3 steps in Example 4 are not intended to imply that 3 chemical transformation steps are considered enough (see Q&A 5.6) in all cases, nor that 3 chemical transformation steps are mandatory. In the case of Example 4, application of the ICH Q11 principles includes control of the enantiomer in the specification of the proposed starting material D, in combination with the understanding that the

			steps immediately prior to D do not impact the impurity profile of the drug substance.
5.4		How should an applicant determine which manufacturing steps impact the profile of mutagenic impurities in the drug substance as part of the selection and justification of starting materials?	As part of determining which manufacturing steps impact the impurity profile of the drug substance, the applicant should first identify mutagenic materials that are likely to be formed or are introduced in the manufacturing process. The applicant can then determine which steps contribute mutagenic impurities to the drug substance at a level considered to impact the impurity profile (see Q&A 5.2). The Hazard Assessment Elements from ICH M7 can be used to determine which of the actual and potential impurities are considered to be mutagenic. For the selection and justification of starting materials, the following approaches are recommended: • Impurities that have been identified in the drug substance ("actual impurities") should be assessed for mutagenicity. • Reagents, solvents, and chemicals used in the synthesis from commercially available chemicals to the drug substance should be assessed for mutagenicity. Note that this will likely include assessment of the mutagenicity of some reagents, solvents, and chemicals that are used in steps before the starting material that is eventually proposed. • Mutagenic substances that are impurities in commercially available precursors or synthetic intermediates, or that are formed as the result of side reactions during the synthesis, could also be present in the drug substance at levels relevant to safety. However, such mutagenic impurities and by-products are usually present at much lower concentrations than reagents, solvents, and intermediates. Therefore, the risk that such impurities will carry over significantly into the drug substance from early reaction steps is lower than for reagents, solvents, or intermediates from the same steps. The applicant should use risk-based reasoning to determine which steps to include in the hazard assessment for this category of potential impurities, and include a discussion of the risk assessment when identifying the point in the synthesis where these impurities and by-products are included in the assessment of mutagenic impurities. • For a starting material that is a commercially available chemical that is introduced late in the

			synthesis of the drug substance (and where its synthetic route is known) the final steps of that chemical's synthesis should be assessed for potential mutagenic impurities. In this case, because the starting material has already been selected based on its commercial availability, the mutagenicity assessment should be used to ensure that the controls on the starting material are adequate. Information collected during the evaluation of potential mutagenic impurities can be submitted in an application and could be valuable for multiple purposes. For example, the justification for a proposed starting material should include information demonstrating that none of the steps immediately upstream (i.e., earlier in the synthesis) of the proposed starting material impact the impurity profile of the drug substance. Also, the suitability of the proposed control strategy can be supported with information about any mutagenic impurities formed or purged in the manufacturing steps between the proposed starting material and the drug substance, or that are controlled in the specification of the proposed starting material. The ICH Q11 exception for impurities that "persist" is also applicable to mutagenic impurities (see Q&A 5.3). In addition, steps involving mutagenic reagents or impurities may be before the starting material if they do not impact the impurity profile of the drug substance (see Q&A 5.5). The approaches outlined in this Q&A are considered to be consistent with the principles in ICH M7, concerning hazard assessment, risk characterisation of mutagenic impurities, and their control. Additionally, this Q&A is not intended for the types of drug substances and indications for which ICH M7 does not apply (e.g., genotoxic drug substances; advanced cancer indications per ICH S9). However, ICH M7 does not provide specific guidance on how mutagenic impurity assessment can be used to justify selection of appropriate starting materials. This Q&A addresses the application of the principles in ICH M7 to the selection and justification of starting materials, based on the ICH Q11 concept of impact to the impurity profile of the drug substance.
5.5		Do all steps that involve mutagenic reagents, impurities, or establish regio- or stereochemical configurations, need to be included in the process description in	No. The ICH Q11 general principles for selection of starting materials do not include a recommendation that all steps involving mutagenic reagents or impurities should be included in the process description in Section 3.2.S.2.2. Similarly, the general principles do not include a recommendation that all steps that establish regio- or stereochemical configurations (which can therefore result in regio- or stereoisomerism) should be included in Section 3.2.S.2.2. However, it is expected that the other ICH Q11 principles on impurities (Q&As 5.2, 5.3 and 5.4) and inclusion of enough of the manufacturing process (Q&A 5.6) be applied when deciding whether steps that

		Section 3.2.S.2.2?	involve mutagenic reagents, impurities, or establish regio- or stereochemical configurations, need to be included. As an example, a mutagenic compound could be introduced prior to the starting material or be the starting material itself provided the ICH Q11 general principles are addressed.
5.6		ICH Q11 states that "*enough of the drug substance manufacturing process should be described in the application*…" What considerations should an applicant apply in the selection of the proposed starting materials to assure that enough of the drug substance manufacturing process will be described in the process description in Section 3.2.S.2.2 of the application?	In deciding whether enough of the drug substance manufacturing process is described in Section 3.2.S.2.2 of the application, the following considerations should be applied: The applicant should <u>first</u> evaluate which chemical transformation steps in the manufacturing process impact the impurity profile of the drug substance. These steps should normally be included in Section 3.2.S.2.2 (Q&As 5.2, 5.3, 5.4). <u>Next,</u> the applicant should examine the steps immediately upstream of those steps that impact the impurity profile of the drug substance. These steps should also be included in Section 3.2.S.2.2 if: • They include a unit operation that has been added to the manufacturing process to control specific impurities that would otherwise impact the impurity profile of the drug substance. Adding multiple purification steps prior to a proposed starting material would not be considered appropriate in order to support its justification. • They need to be carefully controlled (e.g., within narrow parameter ranges) to prevent generation of impurities that would otherwise impact the impurity profile of the drug substance. <u>After</u> these considerations, if the evaluation would result in only a small number of chemical transformation steps, then it is generally appropriate to include one or more additional chemical transformation steps in Section 3.2.S.2.2. This is to ensure that enough steps are conducted under GMP and to mitigate risks associated with contamination and future changes to the synthetic route or supplier of the starting material. The following paragraphs provide further clarification on this risk mitigation and should be considered together. • Although ICH Q11 does not specify how many steps should be performed under GMP, ICH Q11 recommends the inclusion of "*multiple chemical transformation steps*" in Section 3.2.S.2.2 in order to reduce the risk of contamination and support the effective implementation of the control strategy throughout the product lifecycle. When there would be a small number of steps there is an increased risk of contamination that needs to be addressed by the applicant in their starting material justification, and will often be best

			mitigated by including one or more additional steps in Section 3.2.S.2.2. o Potential risks from future changes to the starting material synthesis should also be considered (see Q&A 5.14). In particular, when the proposed starting material is many steps downstream from commercially available chemicals, there is an increased likelihood of changes to its route of synthesis. There is therefore an increased risk that impurities generated in future syntheses may not be detected or purged appropriately if the starting material is only a small number of steps from the drug substance. In order to determine how many additional steps to include, the applicant may also consider other approaches to risk mitigation; for example, inclusion of analytical methodologies in the specification of the proposed starting material that are designed to detect a wide range of possible impurities based on different physical and chemical separation and detection principles and with appropriate acceptance criteria for unspecified impurities. The applicant should include in their justification of the proposed starting material a comprehensive description of what factors were considered in deciding whether enough of the drug substance manufacturing process is provided in Section 3.2.S.2.2 of the application to ensure that risks are appropriately mitigated.
5.7		Should all the ICH Q11 general principles be considered and met in selecting starting materials?	Applicants should consider all of the ICH Q11 principles in the selection and justification of proposed starting materials, rather than selecting just a few principles and using them to justify starting materials. If a proposed starting material does not meet all of the general principles, a rationale should be provided explaining why the starting material is considered appropriate.
5.8		Do the ICH Q11 general principles for selection of starting materials apply to processes where multiple chemical transformations are run without isolation of intermediates?	Yes. The ICH Q11 general principles apply to processes where multiple chemical transformations are run without isolation of intermediates. In the absence of such isolations (e.g., crystallization, precipitations), other unit operations (e.g., extraction, distillation, the use of scavenging agents) should be in place to adequately control impurities and be described in the application. The drug substance synthetic process should include appropriate unit operations that purge impurities. The ICH Q11 general principles also apply for sequential chemical transformations run continuously. Non isolated intermediates are generally not considered appropriate starting materials.

5.9		Do the ICH Q11 general principles for selection of starting materials apply to the selection of starting materials for linear and convergent syntheses?	Yes. The ICH Q11 general principles apply to the selection of starting materials for linear or convergent syntheses. The ICH Q11 general principles should be applied independently to each branch of a convergent synthesis, unless the point of convergence of the branches occurs upstream of an appropriate starting material.
5.10		What considerations are important for starting material specifications?	Applicants should provide and justify a specification (which includes a list of tests, references to analytical procedures, and appropriate acceptance criteria) for all proposed starting materials as part of the control strategy. The specification of a starting material should include tests for identity and purity (e.g., controls on impurities), and could include acceptance criteria for assay, specified, unspecified and total impurities, residual solvents, reagents, elemental impurities and mutagenic impurities. Tests and acceptance criteria should be based on process knowledge and control strategy. The analytical procedures used should be suitably validated. The justification of the specification should include evaluation of the risks and the ability of the subsequent steps to purge impurities.
5.11		For starting materials that are not commercially available chemicals, what information should be provided on the synthetic route?	Information on how the proposed starting material is made (e.g., a flow chart of the starting material manufacturing process, showing all reagents, catalysts and solvents used) should be provided to help justify the controls applied to the starting material. Information about the actual and potential impurities in the proposed starting material should be included.
5.12		What is the difference between a commercially available chemical and a custom synthesised chemical?	ICH Q11 states that "*a commercially available chemical is usually one that is sold as a commodity in a pre-existing, non-pharmaceutical market in addition to its proposed use as starting material"*. A definition of "custom synthesised chemical" was not provided in ICH Q11, but a custom synthesised chemical is generally understood to be one that is made specifically to a drug substance manufacturer's requirement, either in-house or externally, or available for purchase but where the only use is for pharmaceutical manufacture. ICH Q11 makes an important distinction between commercially available chemicals and custom synthesised chemicals. An applicant generally need not justify the use of a commercially available chemical as a starting material, whereas a custom synthesised chemical proposed as a starting

			material should be justified in accordance with the ICH Q11 general principles. The availability of a chemical from multiple suppliers should not be the sole basis for the designation of a chemical as a commercially available starting material. This includes situations where a custom synthesized chemical has become available over time from multiple suppliers. Such chemicals should still be justified according to the ICH Q11 general principles for selection of starting materials. The reference to "*non-pharmaceutical market*" in the ICH Q11 description of commercially available chemicals was included to preclude intermediates from being claimed as commercially available chemicals. It can be acceptable for a starting material that is demonstrated to be a commercially available chemical to enter late in the synthesis, e.g., in the last chemical transformation prior to the drug substance. A chemical manufactured at small scale can be suitable as a commercially available starting material provided that the scale is sufficient for the manufacture of the drug substance and that the chemical is also used in a pre-existing, non-pharmaceutical market. In some cases, a chemical that does not meet the definition of a commercially available chemical (e.g., it does not have a non-pharmaceutical use) but is simple enough in structure may be accepted as a starting material with little justification (e.g., protected natural amino acids as pharmaceutical building blocks).
5.13		What information should be included in the application about a starting material that is a commercially available chemical?	An applicant generally need not justify the use of a commercially available chemical as a starting material (see ICH Q11, Section 5.2.1). However, the applicant should provide basic information (chemical name, chemical formula, and molecular weight), information on the impurity profile, and how the control strategy for the manufacturing process justifies the starting material specification. If the drug substance manufacturer needs to perform additional purification steps to ensure the consistent quality of a commercially available starting material, ICH Q11 also recommends that the additional purification steps should be included in Section 3.2.S.2.2 as part of the drug substance manufacturing process. It is also recognized that on occasion, detailed information on the manufacturing process of a commercially available chemical may not be readily available to the applicant due to restrictions of

			intellectual property. However, well documented synthetic routes that are publicly available can provide important information that should be considered when evaluating potential impurities (e.g., known use of metal catalyst). The applicant should set appropriate controls and should justify the proposed specification for the actual and potential impurities that are reasonably expected in a proposed starting material, based on the scientific knowledge and available information. For all starting materials, applicants should set appropriate controls and be able to justify the proposed specifications.
5.14		Does ICH Q11 include specific guidance for post-approval changes to steps prior to the starting material (e.g., changes in synthetic route, reagents, solvents, starting material supplier)?	No. Post-approval changes to steps prior to starting materials are not explicitly covered in ICH Q11. However, ICH Q11 does describe fundamental science and risk-based concepts that should be used to evaluate the impact of post-approval changes to the process after the starting material (ICH Q11 Section 9 – Lifecycle Management), and these same concepts should be applied to evaluate the impact of changes prior to the starting material. For example, changes prior to the starting material should be evaluated for their impact on the starting material (e.g., on current and potential new impurities, including potentially mutagenic and elemental impurities) and when appropriate on the drug substance. The evaluation could be based on risk assessment and scientific understanding of the proposed change and its proximity to the starting material. The evaluation should include an assessment of the control strategy (e.g., adequacy of the specification for the starting material, including analytical procedures' abilities to detect any new impurities). As stated in ICH Q7 Q&A document Section 13.1, each party in the supply chain is responsible for transferring information related to quality or regulatory changes to the next customer in the supply chain so that the information is transferred along the supply chain to the drug product manufacturer in a timely manner. Post-approval changes to information on the starting material should be reported to regulatory authorities in accordance with regional regulations and guidelines.
5.15		Can the lifecycle section of ICH Q11 apply to Lifecycle Management of Starting Materials?	Yes. In addition to what is submitted in the application, the applicant's Pharmaceutical Quality System (PQS) should address residual risks to the drug substance quality associated with future changes upstream of the defined starting material. The Lifecycle Management section of ICH Q11 reinforces management's responsibility described in ICH Q10, which is applicable to starting material lifecycle management. ICH Q10 Section 2.7

			(Management of Outsourced Activities and Purchased Materials) recommends that '*The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials*'. ICH Q7 Sections 7 (Materials Management) and 13 (Change Control), ICH Q7 Q&A document Sections 7 and 13, as well as ICH Q10 Section 2.7 (Management of Outsourced Activities and Purchased Materials) provide guidance that can be applied to the management of starting materials and starting material suppliers. ICH Q9 and its Annexes provide guidance on the use of principles for quality risk management which can be applied to future changes related to the starting materials (e.g., new starting material suppliers, manufacturing processes, or specifications).
5.16		Is a "*starting material*" as described in ICH Q11 the same as an "API starting material" as described in ICH Q7?	Yes. ICH Q11 states that the Good Manufacturing Practice (GMP) provisions described in ICH Q7 apply to each branch of the drug substance manufacturing process beginning with the first use of a "*starting material*". ICH Q7 states that appropriate GMP (as defined in that guidance) should be applied to the manufacturing steps immediately after "API starting materials" are entered into the process (see ICH Q7 Q&A Question 1.1). Because ICH Q11 sets the applicability of ICH Q7 as beginning with the "*starting material*", and ICH Q7 sets the applicability of ICH Q7 as beginning with the "API starting material", these two terms are intended to refer to the same material. ICH Q7 states that an "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API. ICH Q7 provides guidance regarding good manufacturing practices for the drug substance; however, it does not provide specific guidance on the selection and justification of starting materials. When a chemical, including one that is also a drug substance, is proposed to be a starting material, all ICH Q11 general principles still need to be considered.

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6. CONTROL STRATEGY

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

7. PROCESS VALIDATION/EVALUATION

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

8. SUBMISSION OF MANUFACTURING PROCESS DEVEOPMENT AND RELATED INFORMATION IN THE COMMON TECHNCICAL DOCUMENT (CTD) FORMAT

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

9. LIFECYCLE MANAGEMENT

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

10. ILLUSTRATIVE EXAMPLES

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section (see Q&A 5.3)	

11. GLOSSARY

#	Date of Approval	Questions	Answers
N/A	**N/A**	No Q&A drafted on this section	

ANNEX: Q&As linked to the respective Sections of ICH Q11 Guideline

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