Guidelines for

The Quality Part Module 3 Part S

Drug Substance

January 2017

Table of contents

Introduction

The Quality guideline provides a harmonized structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration application based on Good Manufacturing Practice (GMP) risk management. It defines criteria for the validation of the two most common types of analytical procedures: qualitative and quantitative tests for active substance and impurities (organic and inorganic impurities and residual solvents) in Active Pharmaceutical Ingredient-API.

The Quality module for the drug substance defining the validation parameters needed for a variety of analytical methods of control and describing characteristics to be considered for the validation of analytical procedures are included in a marketing authorization application (MAA).

This document is intended to provide a global policy and guidance for the preparation of the Quality module of Drug Substance for an application file that meet with the requirement of Ministry of Public Health in Lebanon.

Drawing upon the reviewed files, we are including a rubric on the answers of the Frequently Asked Questions (FAQ) that had been received from several manufacturers.

The document must be presented in pdf form and not in the form of pictures such as scan, paint, jpeg, etc.

The manufacturer should provide all information for the different sections including the closed part of the DMF. The Certificate of Suitability (COS) could substitute any document classified in the closed part. However, even if the COS is presented, the parts 3.2.S.6 and 3.2.S.7 must be provided.

Information and requirements

As defined in the scope of the ICH Guidelines, information and requirements described below are intended to facilitate the handling and assessment of submissions.

When more than one drug substance is used in a drug product, information should be presented separately as one complete Drug Substance section.

The activities and outputs which need to be addressed for the registration file include:

Section	Title	Requirements	Answer to FAQ
3.1.	Table of content of module 3	A Table of Contents for the filed application should be provided	
3.2.	Body of Data	Indicates where the information should be located	
3.2.S	Drug Substance		
3.2.S.1	General Information	Name, Manufacturer	
3.2.S.1.1	Nomenclature	- Chemical Abstracts Service (CAS) registry number - Recommended International Nonproprietary Name (INN) - Chemical name (s)	
3.2.S.1.2	Structure	The structural formula, including relative and absolute stereochemistry, the molecular formula, the relative molecular mass and chirality should all be provided	
3.2.S.1.3	General Properties	A list should be provided of physicochemical and other relevant properties of the drug substance: pH / pKa, melting point, solubility, Hygroscopicity, physical form, crystalline form, etc. List the polymorphic form(s) present in the proposed active.	**Q1.** How much detailed information on the general properties of the drug substance should be included in 3.2.S.1.3? **A1.** A list of physicochemical and

			other relevant properties of the drug substance, including biological activity, should be included in 3.2.S.1.3. The information on general properties should be provided only for the form of the drug substance used in the drug product, not possible alternative forms (e.g., polymorphs). More detailed information on the properties of the drug substance, including possible alternative forms, should be included in 3.2.S.3.1.
3.2.S.2	Manufacture		
3.2.S.2.1	Manufacturer(s) (name, manufacturer)	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided	
3.2.S.2.2	Description of Manufacturing Process and Process Controls	A flow diagram of the synthetic process (es) and a sequential procedural narrative of the manufacturing process should be submitted. *-The narrative should include quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time)*	**Q1.** Should information on process controls be provided in section 3.2.S.2.2 or 3.2.S.2.4? **A1.** All process controls should be identified in 3.2.S.2.2. For critical controls, additional information should be provided in 3.2.S.2.4.
3.2.S.2.3	Control of Materials	Information on the quality and control of Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. *-For biologically-sourced materials, this should include*	**Q1.** Where should analytical procedures for materials described in 3.2.S.2.3 be included? **A1.** The analytical procedures for the control of materials (e.g., starting materials, reagents, raw

		information regarding the source, manufacture, and characterization.	materials, solvents) should be presented in section 3.2.S.2.3.
3.2.S.2.4	Controls of Critical Steps and Intermediates	Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process should be provided	**Q1.** Should batch data for intermediates or critical steps be included in 3.2.S.2.4? **A1.** Batch data, together with analytical procedures and acceptance criteria for intermediates or critical steps, would be presented in 3.2.S.2.4.
3.2.S.2.5	Process Validation and/or Evaluation	Process validation and/or evaluation studies for aseptic processing and sterilization should be included. The aseptic process may be recorded through a comprehensive documentation : - *Suitable testing facilities, equipment, instruments and methodology (properly installed, qualified and maintained) should be available* - *Suitable clean room facilities should be available, in terms both of the "local" and "background "environments. Assurance that the Clean Room environment is as specified should be secured through the implementation of a program of retesting, in-process control and monitoring*	**Q1.** Where should justification for reprocessing be included? **A1.** If justification for reprocessing is warranted by a regional authority, the information would be included as part of the description of the manufacturing process in 3.2.S.2.2. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.S.2.4. If validation information is warranted, the validation information should be included in 3.2.S.2.5.
3.2.S.2.6	Manufacturing Process Development	A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance -*Reference should be made to the drug substance data provided in section 3.2.S.4.4.*	
3.2. S.3.	Characterization		
3.2.S.3.1	Elucidation of Structure and other	Confirmation of structure based on synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of	**Q1.** Where should the list of polymorphs be included? **A1.** Total number of polymorphs

	Characteristics	stereochemistry, or the potential for forming polymorphs should also be included.	should be listed here and those intended to form the active should be summarized in 3.2.S.1.3.
3.2.S.3.2	Impurities	Information on impurities should be provided include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures. - *Organic impurities (process- and drug-related)* - *Inorganic impurities* - *Residual solvents*	**Q1.** Should structural characterization data and a summary of the method of preparation of impurities be included in 3.2.S.3.2? **A1.** This information should be included in 3.2.S.3.2. Characterization of impurity reference standards should be provided in 3.2.S.5. **Q2.** Where chromatograms should be provided for impurities? **A2.** ICH Q3A identifies the chromatograms as part of the analytical validation studies. Therefore, relevant chromatograms should be included in 3.2.S.4.3. **Q3.** Should data on impurities reported in batch analyses be included in 3.2.S.3.2 or 3.2.S.4.4? **A3.** Data on observed impurities for relevant batches should be provided in 3.2.S.3.2.
3.2.S.4	Control of Drug Substance		
3.2.S.4.1	Specification	A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other	**Q1.** If alternative analytical procedures are used to control the drug substance, should they also be

		criteria for the tests described. - *A copy of monograph should be provided including : Description, identification, assay and impurities*	listed in the specification **A1.** Any analytical procedure used to control the drug substance, and the associated acceptance criteria, should be listed in the specification.
3.2.S.4.2	Analytical Procedures	The analytical procedures used for testing the drug substance should be provided. *The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:* *- Identification tests;* *- Quantitative tests for impurities' content;* *- Limit tests for the control of impurities;* *- Quantitative tests of the active moiety in samples of drug substance*	**Q1.** Should an analytical procedure that is only used for stability studies be included in 3.2.S.4.2? **A1.** Information on analytical procedures that are used only for stability studies should be included in 3.2.S.7 **Q2.** If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)? **A2.** The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P because the sample preparation, at least, will differ.
3.2.S.4.3	Validation of Analytical Procedures	Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.	
3.2.S.4.4	Batch Analyses	Description of batches and results of batch analyses should be provided. *All residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based*	**Q1.** Where collated data for a test from multiple batch analyses should be presented? **A1.** If collated data from batch analyses is warranted, the data

		requirements.	should be presented in 3.2.S.4.4.
3.2.S.4.5	Justification of Specification	Justification for the drug substance specification should be provided - *A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.*	
3.2.S.5	Reference Standards or Materials	A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. - *All analytical results of reference standard, or reference material used as reference substance should be provided*	
3.2.S.6	Container Closure System	A description of the container closure system(s) should be provided, including the identity of materials of construction of each packaging component, and their specifications. - *The suitability should be briefly discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.*	
3.2.S.7	Stability	Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. - *Conclusions with respect to storage conditions and retest date or shelf-life, as appropriate should be provided.* - *Post-approval Stability Protocol and Stability Commitment should be provided*	

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

**It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.*

***If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.*

Reference:

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2002, Common Technical Document, Quality Guidelines (M4Q (R1)