IFPMA

Suggested template for

Description of differences in CTD M3 (CMC) for MAAs and / or CMC post-approval changes

Purpose of this document

This document aims to act as a reviewer's aid to facilitate reliance activities for Marketing Authorization Applications (MAAs) and/or post-approval changes (PACs), specifically focusing on Chemistry, Manufacturing, and Controls (CMC), for all types of medicinal products submitted. The template aims to provide comprehensive information and justifications for any variations or discrepancies in the registered documentation compared to the reference National Regulatory Authority (NRA).

Background

According to the WHO[1], reliance can only be applied if the relying NRA that intends to use a foreign assessment as the basis for its own assessment and regulatory decision making has the assurance that the medical product being assessed is essentially the same as the one submitted to the reference NRA. Furthermore, the impact of any differences should be assessed and justified by the Applicant, i.e. the manufacturer or Marketing Authorization Holder.

As stated in IFPMA's position paper on product sameness[2], "multinational companies supply products of the same quality to all countries and do not provide different "versions" of product quality to different countries," however, as MAA submission content is not fully harmonized around the world, this means that there can be differences in data and documentation requirements between the reference NRA and the relying NRA. For example, there can be differences such as additional country-specific information submitted for review, e.g. product stability data according to the stability climatic zone, and there may also be additional exceptions such as different supply chains. This document aims to help highlight these exceptions to the relying NRA to support a targeted/abridged review of information/data that has not been previously reviewed by the reference NRA in the original application. Accompanying explanations of the differences and a justification (including reference to the location of any supportive data, as appropriate) are also provided in this document where needed.

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[1] WHO (2021) "Good reliance practices in the regulation of medical products"

[2] IFPMA (2021) "The importance of sameness of product in the context of regulatory reliance"

This document is to be completed by the Applicant to facilitate the use of reliance and communicate potential information/data differences compared to the approval of the reference NRA**.**

Template part I: General information

Product Name*:
Date of original approval:
Pharmaceutical form:
Strength(s):
Active Pharmaceutical Ingredient:
Reference Regulatory Authority:
Reference NRA Product Registration Information (e.g. License number, Date):
MAA or PAC Applicant** (same company/group as reference NRA?: Yes, No or add explanation):
Subject of the application(s):

**Please indicate if different name*

***Usually this will be the same company, group or companies as for the reference agency. If this is not the case, (e.g. local agent under contract) please add an explanation.*

Template part II: Dossier sameness

It is intended that the data submitted in this application has already been reviewed and approved by the Reference NRA. In some circumstances, the dossier submitted to the relying NRA may contain the same CMC information but slightly fewer details than the product approved by the reference NRA due to different approaches in handling variations between NRAs around the globe or different regulations / legal requirements in each country, e.g. testing sites do not need to be registered in all NRA's. Therefore, unless identified in the table below, the details in these CTD components have already been reviewed by the reference NRA, i.e. dossier sameness is being claimed compared to the reference NRA.

Furthermore, where dossier sameness is claimed in the table below, the product will be manufactured to the same quality standards as the reference NRA, unless specifically identified.

Template part III: Summary of CMC differences compared to the reference NRA

Modules and numbering reflect the ICH Common Technical Document (column A) and are listed in the table below. The table can be expanded or reduced to meet the needs of the submission, e.g. some products may have multiple drug substance sections. For all modules/sub-modules which are part of this submission, an X has been used to identify the overall content of the submission package (column B). Modules/sub-modules in Column C include a ***YES*** if the information/data is the same as in the dossier filed with the reference NRA in line with the outline on dossier sameness above. Modules/sub-modules include a ***NO*** if information/data is included in the dossier that has not been reviewed by the reference NRA. In the case of ***NO***, a summary of the differences and a justification are provided (column D).

Note: *The table included within this document contains some sections filled out with illustrative examples (section 3.2.P.3 & 3.2.P.5). These examples aim to demonstrate how we envision the table to be completed, showcasing the type of information and level of detail expected.*

COLUMN A	COLUMN B	COLUMN C	COLUMN D
Module 3/Submodule	**Documents included in this application**	**Dossier sameness as compared to Reference NRA (Yes/No)**	**Brief discussion and justification that the difference has no impact on product quality (including reference to supporting data as appropriate)**
3.2.S DRUG SUBSTANCE			
3.2.S.1 General Information			
3.2.S.2: Manufacturer			
3.2.S.2.1: Manufacturer			
3.2.S.2.2: Description of Manufacturing Process and Process Controls			
3.2.S.2.3: Control of Materials			
3.2.S.2.4: Controls of Critical Steps and Intermediates			
3.2.S.2.5: Process Validation and/or Evaluation			
3.2.S.2.6: Manufacturing Process Development			
3.2.S.3 Characterization			
3.2.S.3.1: Elucidation of Structure and other Characteristics			

3.2.S.3.2: Impurities			
3.2.S.4: Control of Drug Substance			
3.2.S.4.1: Specification			
3.2.S.4.2: Analytical Procedures			
3.2.S.4.3: Validation of Analytical Procedures			
3.2.S.4.4: Batch Analyses			
3.2.S.4.5: Justification of Specification			
3.2.S.5 Reference Standards or Materials			
3.2.S.6 Container Closure System			
3.2.S.7 Stability			
3.2.S.7.1: Stability Summary and Conclusion			
3.2.S.7.2: Post-approval Stability Protocol and Stability Commitment			
3.2.S.7.3: Stability Data			
3.2. P. DRUG PRODUCT			
3.2.P.1 Description and Composition of the Drug Product			
3.2.P.2. Pharmaceutical Development			
3.2.P.3: Manufacture			
3.2.P.2.1: Manufacturer	*YES*	*NO*	*Finished drug product release site is different from EU. EU regulations specify that the qualified person shall certify that each batch underwent analysis in an EU Member State. Therefore the finished product release site for the EU market has to be in EU territory, which is different from that for rest of the world. The same release criteria and release procedure are applied to all release sites to ensure that the products have identical quality*
3.2.P.2.2: Batch Formula	*YES*	*YES*	

3.2.P.3.3: Description of Manufacturing Process and Process Controls			
3.2.P.3.4: Controls of Critical Steps and Intermediates			
3.2.P.3.5: Process Validation and/or Evaluation			
3.2.P.4: Control of Excipients			
3.2.P.4.1: Specification			
3.2.P.4.2: Analytical Procedures			
3.2.P.4.3: Validation of Analytical Procedures			
3.2.P.4.4: Justification of Specifications			
3.2.P.4.5: Excipients of Human or Animal Origin			
P.4.6: Novel Excipients			
3.2.P.5. Control of Drug Product			
3.2.P.5.1: Specification	*YES*	*NO*	*No change in test items, but US version contains US specific adaptations*
3.2.P.5.2: Analytical Procedures	*YES*	*NO*	*Updated to align with P.5.1*
3.2.P.5.3: Validation of Analytical Procedures	*YES*	*YES*	
3.2.P.5.4: Batch Analyses	*YES*	*YES*	
3.2.P.5.5: Characterisation of Impurities	*YES*	*YES*	
3.2.P.5.6: Justification of Specification	*YES*	*NO*	*Updated with primary stability data from additional time points in accordance with the stability protocol*
3.2.P.6: Reference Standards or Materials	*YES*	*YES*	

3.2.P.7: Container Closure System	*YES*	*YES*	
3.2.P.8: Stability			
3.2.P.8.1: Stability Summary and Conclusion			
3.2.P.8.2: Post-approval Stability Protocol and Stability Commitment			
3.2.P.8.3: Stability Data			
3.2.A: APPENDICES			
3.2.A.1: Facilities and Equipment			
3.2.A.2: Adventitious Agents Safety Evaluation			
3.2.A.3: Excipients			

Signature:…….

Date:……

Name:……

Job Title:…….