ipec EUROPE

INTERNATIONAL PHARMACEUTICAL EXCIPIENTS COUNCIL

IPEC EUROPE PROPOSED OUTLINE FOR AN EXCIPIENT MASTER FILE SYSTEM IN EUROPE

Introduction

IPEC Europe is advocating the use of a partially closed master file system for excipients (EMF) in Europe similar to the current EU Active Substance Master File (ASMF). The rationale for proposing such a system is discussed in detail in the accompanying paper "IPEC Europe Approach to the Lack of a Master File System for Excipients in Europe" (of 21 December 2009).

Scope

It is proposed that the use of an EMF would be a **voluntary approach** for the excipient manufacturer allowing him to protect his confidential information within the Closed Part of the master file. It is intended that the excipient user/ Marketing Authorisation Holder (MAH) would have access to all the information needed to take full responsibility for its intended use in their drug product in the Open Part of the EMF.

IPEC Europe considers that an EMF would only be of value for certain cases. In practice this is expected to apply **mainly to novel excipients**[1], and in general would **not** be necessary for compendial excipients, for which a Certificate of Suitability (CEP) that can be granted by the EDQM.

Contents

The format of the EMF could be based on that proposed by the European Medicines Agency (EMA) in its "Guideline on Active Substance Master File Procedure"[2]. Annex 1: Table 1 of this guideline provides an overview of contents of the Open (Applicants) and Closed (Restricted) Parts of a European Drug Master File (EDMF). It is suggested that this structure could be applied to excipients as presented in Table 1 below. In addition to the quality data as outlined in the table, safety information on the excipient (if available) could also be presented in the Open Part of the EMF by inclusion in separate nonclinical (as Module 2.4 Nonclinical Overview) and clinical (as Module 2.5 Clinical Overview) sections. Alternatively the safety information could be presented by the MAH in the relevant sections of their Marketing Authorisation Application (MAA) only.

Management

IPEC Europe suggests that an EMF system could be managed in the same way as is currently practised for ASMFs and is explained in the EMA's "Guideline on Active Substance Master File Procedure (as previously referenced). Like an ASMF, an EMF would only be submitted to the EMA (for a Centralised Application) or Competent Authorities (for Mutual Recognition or National Applications) in support of a MAA or Marketing Authorisation Variation (MAV). Accordingly any fees for the EMF assessment would be paid by the Applicant/MAH as part of the MAA/MAV approval procedure (see also 3AQ7a "European Drug Master File Procedure for Active Substances" May 1993, section 13). Changes and updates to EMFs could be managed as described for ASMFs (see EMA's "Guideline on Active Substance Master File Procedure", section 5) with EMF holders obliged to notify both the Applicant/MAH(s) and the EMA/Competent Authority(ies) of changes to the Open Part or just the EMA/Competent Authority(ies) of changes to the Closed Part only as applicable. In the former case, it would then be the responsibility of the MAH to report the EMF change in relation to their product by means of an appropriate variation procedure if required.

---

[1] I.e. those referred to in the EU Notice to Applicants Volume 2B[1] – paragraph 3.2.P.4.6 - as: "*[…] excipient(s) used for the first time in a drug product or by a new route of administration […]*".
See: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

[2] (Ref.: EMEA/CVMP/134/02-Rev.2; CPMP/QWP/227/02-Rev.2)

Table 1: Suggested Contents of EMF (based on EMA's ASMF Guideline Annex 1)

NtA CTD Section		Open (Applicants) Part	Closed (Restricted) Part
3.2.S.1	**General Information**		
3.2.S.1.1	Nomenclature	Yes	
3.2.S.1.2	Structure	Yes	
3.2.S.1.3	General Properties	Yes	
3.2.S.2	**Manufacture**		
3.2.S.2.1	Manufacturer(s)		
3.2.S.2.2	Description of Manufacturing Process and Process Controls	Yes – brief description and flow chart	Yes – detailed information
3.2.S.2.3	Control of Materials	No	Yes
3.2.S.2.4	Control of Critical Steps and Intermediates	No	Yes – in line with more detailed information in 3.2.S.2.2
3.2.S.2.5	Process Validation and/or Evaluation	Yes - brief evidence that process is suitably validated	Yes – detailed information
3.2.S.2.6	Manufacturing Process Development	No	Yes
3.2.S.3	**Characterisation**		
3.2.S.3.1	Elucidation of Structure and other Characteristics	Yes	No
3.2.S.3.2	Impurities	Yes – at appropriate level of detail for user/MAH use	Yes - in line with more detailed information in 3.2.S.2.2
3.2.S.4	**Control of Drug Substance**		
3.2.S.4.1	Specification	Yes	No
3.2.S.4.2	Analytical Procedures	Yes	No
3.2.S.4.3	Validation of Analytical Procedures	Yes	No
3.2.S.4.4	Batch Analysis	Yes	No
3.2.S.4.5	Justification of Specification	Yes	Yes - in line with more detailed information in 3.2.S.2.2
3.2.S.5	**Reference Standards or Materials**	Yes	No
3.2.S.6	**Container Closure System**	Yes	No
3.2.S.7	**Stability**		
3.2.S.7.1	Stability Summary and Conclusions	Yes	No
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	Yes	No
3.2.S.7.3	Stability Data	Yes	No

16 September 2010