Medicinal Dossier guidance

For devices which incorporate an ancillary medicinal substance and fall under Rule 14 of EU 2017/745 (MDR)

bsi.

By Royal Charter

Introduction

For devices which incorporate an ancillary medicinal substance and fall under **Rule 14 of EU 2017/745 (MDR)**, the quality, safety and usefulness of the substance shall be verified by analogy with the methods specified in **Annex I of Directive 2001/83/EC** (Medicinal Products Directive). **Annex IX, 5.2(a)** of the MDR states the Notified Body should seek a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or from the EMA, on the quality and safety of the substance including the benefit or risk of the incorporation of the substance into the device.

Annex II, Section 6.2 (a) of the MDR states the technical documentation shall identify the source of that substance and contain the data of the tests conducted to assess its safety, quality and usefulness, taking into account the intended purpose of the device.

To perform their assessment, the Medicines Competent Authorities (CA) prefer the documentation to follow the Common Technical Document (CTD) format. CTD is the format used for pharmaceutical assessment of medicinal products. Complying with the this format, facilitates the CA review.

Scope of this document

The purpose of this document is to guide the manufacturer in the preparation of this documentation based on information provided by the various Competent Authorities. Note that Competent Authorities may have slightly different requirements and where the Competent Authority is known, specific advice may be available on their websites.

MEDDEV 2.1/3 Rev.3 is the official guidance on the content of the medicinal dossier. This BSI guide is intended to supplement the official guidance based on information published by the Competent Authorities as well as, feedback from ancillary substance reviews conducted by BSI. MEDDEV 2.1/3 is expected to be superseded by a MDCG document in the future and once available should be consulted by the manufacturers.

Note: the phrase “ancillary medicinal substance” is used throughout this document. This document also applies for ancillary human blood derivatives. Where there are specific differences these are highlighted.

Document requirements

In order to facilitate review, typically performed by a quality, a non-clinical and a clinical assessor, it is necessary to provide the Medicinal Dossier as separate, indexed and searchable modules (PDF). Each module should be less than 100 MB to comply with Competent Authority requirements. If necessary, supportive information can be provided in Appendices to the Modules. An index showing the folder structures and document titles should be also provided. See reference section below for more detailed guidance, in particular the **EMA dossier guidance**.

Module 1 - Administrative Information and Prescribing Information	
Introduction	A general description of the device, including the justification regarding purpose of incorporation of the ancillary medicinal substance in the medical device, in particular its ancillary nature, together with a critical evaluation of results of the risk assessment and an assessment of benefit risk of the ancillary substance.
GMP declaration	A declaration from the manufacturer of the medical device must also be submitted stating that the integral substance has been produced under Good Manufacturing Practices (GMP) requirements. It is recommended by some Competent Authorities that this declaration is drawn up in line with the Qualified Person's (QP) declaration. For Active pharmaceutical ingredients (APIs) a justification of the quality, if not manufactured in accordance with GMP requirements, should be provided.
Labelling and IFU	A copy of the labelling, including IFU. These should be clear and searchable.

Module 2 - Common Technical Document (CTD) Module summaries	
Quality overall summary	The aim of this section is to provide expert summaries of the information on the ancillary medicinal substance, overviews of the quality sections, non-clinical and clinical sections.
Non clinical summary	This module is expected to contain a clinical summary which focuses on a discussion of the clinical usefulness of the integral medicinal substance, on the rationale for inclusion in the medical device and on the safety of this substance.
Clinical summary	

Module 3 - Quality

Can be split into two documents as described in the following tables

Module 3 - Drug substance	
Drug substance information	If the ancillary substance has a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP), a copy of the current, signed CEP declaration should be included. If the ancillary substance has an Active Substance Master File (ASMF), a copy of the applicant's part of the ASMF should be included together with a signed "Letter of Access" to the closed part. If ASMF or CEP are not available, the information of the ancillary substance should be structured according to **Module 3.2.S** of the Common Technical Document (CTD) -format. **See Annex I of EMA guideline on active substance master file procedure**. All headings should be included. If not applicable, state this, with a rationale, rather than removing the section. Where applicable, reference shall also be made to the European Pharmacopoeia (Ph Eur) or in the absence of a Ph Eur monograph to a national pharmacopoeia of one of the Member States (e.g., for reference standards or test methods). If no monograph is available from the Member States, reference may be to other national monographs or to the manufacturer's specification and methods of analysis and a justification should be provided. For ancillary human blood derivatives for which a Plasma Master File (PMF) already exists, the relevant information in module 3, already submitted as part of the PMF, does not need to be provided with the application dossier for the consultation procedure. In this case, a notification letter from the manufacturer should accompany module 3. This letter should also include a declaration that the manufacturer will be informed of any changes to the manufacture of the ancillary human blood derivatives and a declaration that the PMF holder has submitted the PMF certificate, evaluation report and PMF dossier to the manufacturer. GMP certification, less than 3 years old, (or equivalent quality certification) should be provided for the substance manufacturing site(s).

Note: in CTD the term drug product is used. In this case it refers to medical device with ancillary medicinal substance. The information on the incorporation of the ancillary substance in the device may include the following CTD headings.

Module 3 - Drug product - Medical device with ancillary medicinal substance	
3.2.P.1 Description and composition of the drug product	A description of the device and its composition should be provided, including the quantitative details of the ancillary substance.
3.2.P.2 Pharmaceutical development	This section should cover development of the device, including choice of the ancillary substance. The composition of the device and any excipients used should be stated. Also a summary of the packaging and materials should be included.
3.2.P.3 Manufacture	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. The quality system of each manufacture should be included. Certificates may be placed in the appendix. A flow chart and description of the manufacturing process including batch size, in-process tests and critical process parameters should be listed.
3.2.P.4 Control of excipients	Excipients involved in the application of the ancillary substance, for example to aid with coating or ensure a specific release rate should be listed, together with their specifications. The control of excipients (or materials) related only to the device rather than the ancillary substance, (e.g. dressing layers, or stent delivery materials) do not need to be described in this document.
3.2.P.5 Control of drug product	3.2.P.5.1 The specifications and tests from incoming goods, in-process tests and final release should be listed. 3.2.P.5.2 The test methods should be specified. 3.2.P.5.3 Validation of test methods used. 3.2.P.5.4 Batch data from 3 recent production scale batches should be included. 3.2.P.5.6 A justification of the specification for the tests used for the ancillary medicinal substance should be included.
3.2.P.6 Reference standards or materials	Any reference standards used in the testing of the ancillary substance should be included. Justification should be provided if PhEur standards are not used.

Module 3 - Drug product - Medical device with ancillary medicinal substance	
3.2.P.7 Container closure system	A description of the primary and secondary packaging. This will be assessed, for the device, by the Notified Body; however, the Competent Authority will need to understand the packaging requirements related to the medicinal substance.
3.2.P.8 Stability	Include a clear statement of the claimed shelf life of the device and if applicable, any in-use shelf-life. Include stability protocols, reports and data relevant for the ancillary medicinal substance stability. If relevant, the fate of known impurities on stability should also be discussed.

Module 4 - Nonclinical Study Reports	
Biocompatibility	Data used to support biocompatibility of the device may be used here. The purpose of this module is to provide a critical assessment of the non-clinical safety of the ancillary substance, which should as a minimum include , pharmacology/ pharmacodynamics, pharmacokinetics and toxicology including local tolerance. Relevant literature and pre-clinical testing related to the ancillary substance should be included in this module.

Module 5 - Clinical Study Reports	
CER	The Clinical evaluation report (CER) may be used to support clinical data. However, the purpose of the review is to assess the risk benefit of the ancillary medicinal substance, not the device as a whole. Therefore, it is useful if the CER is supplemented by a document directing the reviewer to the clinical data which is directly important for substantiating the safety and usefulness of the integral substance. This may take the form of literature or clinical data. A conclusion on the risk/ benefit of adding the ancillary substance to the device should be included. If the device covers multiple strengths or indications, risk-benefit for each variant should be included.

Useful references

The references below are useful as further reading when collating the medicinal dossier and have been used for the creation of this document.

Title	Description
MEDDEV 2.1/3 Rev. 3	Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative. **Note:** MEDDEV 2.1/3 Rev.3 is expected to be superseded by an MDCG document.
EMA dossier requirements	European Medicines Agency dossier requirements.
EMA Consultation procedure for ancillary medicinal substances in medical devices	Overview and further links from EMA for Consultation procedure for ancillary medicinal substances in medical devices.
EMA Presentation and format of the dossier Common Technical Document (CTD)	EudraLex Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD). Comprehensive description of CTD dossier, modules and sub-sections to be used **(ICH guideline M4 (R4))**.
EMA Guideline on Active Substance Master File	Guideline on Active Substance Master File procedure (EMEA/CVMP/134/02 Rev 3/Corr; CPMP/QWP/227/02 Rev 3/Corr). Please note this guideline is not applicable for biological active substances.

Note: Some Medicines Competent Authorities have dossier requirements listed on their websites. If the Competent Authority is known, the manufacturer is encouraged to consult this as well.

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