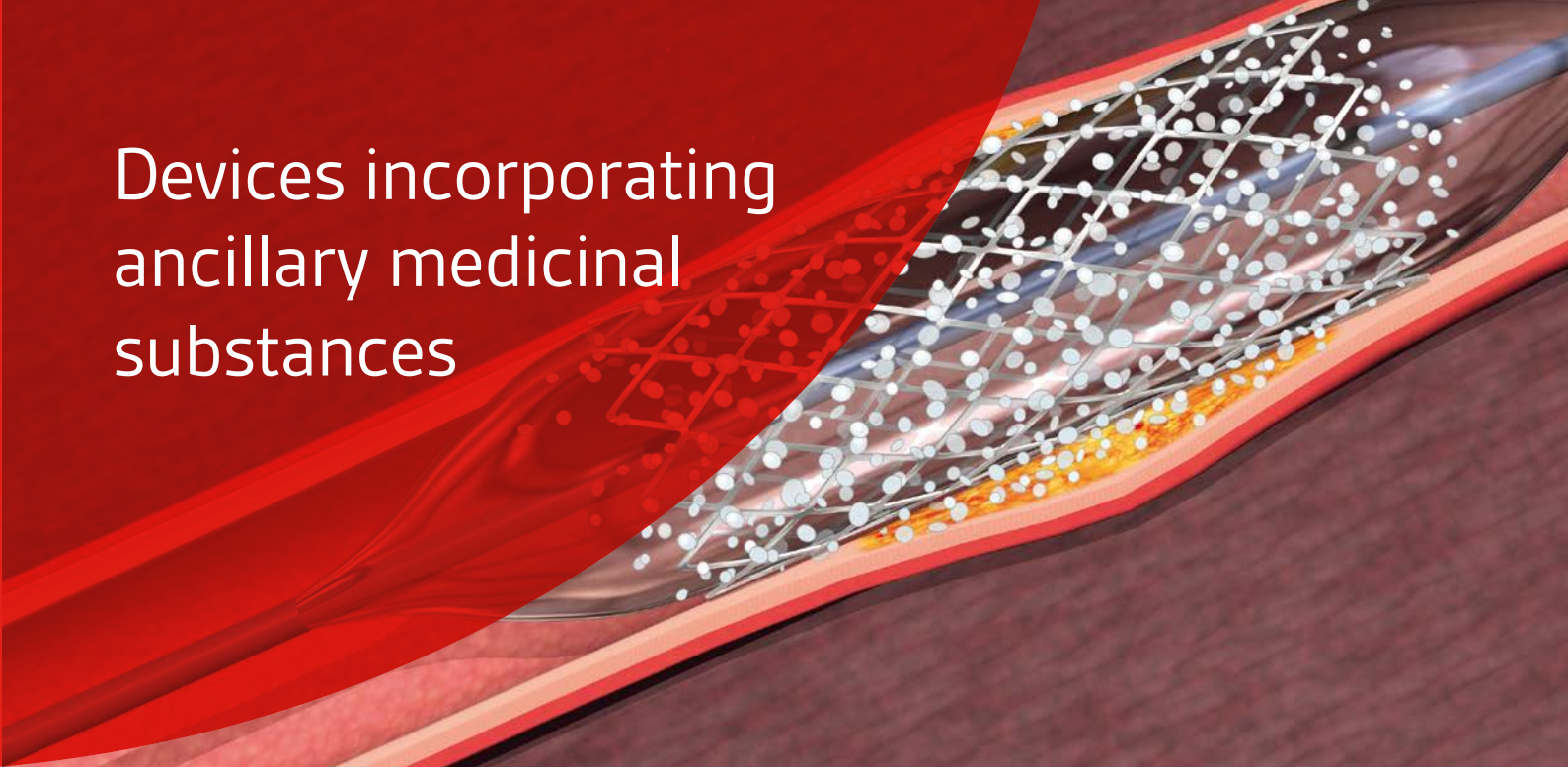
Devices incorporating ancillary medicinal substances



Medicinal dossier guidance

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

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 to Directive 2001/83/EC (the 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) states the documentation shall identify the source of that substance and contain the data of the tests conducted to assess its safety, quality and usefulness, taking account of the intended purpose of the device.

In order to perform their assessment, the Medicines Competent Authorities (CA) prefer the documentation to follow the Common Technical Documentation (CTD) format. CTD is the format used for pharmaceutical assessment of medicinal products and use of this format facilitates the CA review.

Scope of this document

The purpose of this document is to guide the device manufacturer in the preparation of this documentation based on information provided by the various Competent Authorities. Please note different Competent Authorities may have slightly different requirements and where the Competent Authority is known, specific advice may be available on their websites or via the BSI Medicinal team.

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 on behalf of device manufacturers. MEDDEV 2.1/3 is expected to be superseded by a MDCG document in the future and once available should be consulted by the manufacturers.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.

Documentation Requirements

In order to facilitate review, typically performed by a quality, a non-clinical and a clinical assessor; it is necessary to provide the dossier as separate, indexed and searchable (pdf) modules. 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 provided. See reference section below for more detailed guidance, in particular the EMA dossier guidance.

Module 1 Introduction	
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	In module 1 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 be drawn up in line with the QP declaration. For non-traditional 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. This should be clear and searchable.

Module 2 CTD Module Summaries	
Quality overall summary	The content 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. Module 2 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..
Non clinical summary	
Clinical summary	

Module 3 Quality Documentation, 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 CTD-format. See Annex I of CPMP/QWP/227/02 Rev 3/Corr. All headings should be included. If not applicable, state this, with a rationale, rather than remove 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. For example, 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 should accompany module 3 from the medical device manufacturer. This letter should also include a declaration that the device 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 medical device manufacturer. GMP certification, less than 3 years old, (or equivalent quality certification) should be provided for the substance manufacturing site(s).

Module 3 –– Drug Product (Medical device with ancillary medicinal substance)

Note in CTD documentation 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
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.

Module 3 Drug Product (Medical device with ancillary medicinal substance) – *Continued*	
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.
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 from the medicinal substance point of view.
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 Non-clinical data	
Module 4	Data used to support biocompatibility of the device may be used here. The purpose of this section 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 section.

Module 5 Clinical data	
Module 5	The 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 in the creation of this document.

Title	Link	Description
MEDDEV 2.1/3 rev 3	http://www.meddev.info/_documents/2_1_3_rev_3-12_2009_en.pdf	Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative. Note this document is expected to be superseded by a MDCG document in 2021.
EMA dossier requirements	https://www.ema.europa.eu/documents/regulatory-procedural-guideline/ema-recommendation-procedural-aspects-dossier-requirements-consultation-ema-notified-body-ancillary_en.pdf	European Medicines Agency dossier requirements.
EMA Consultation procedure for ancillary medicinal substances in medical devices	https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices/consultation-procedure-ancillary-medicinal-substances-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.
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.	EMA Guideline on Active Substance Master File.

Note some Medicines Competent Authorities have dossier requirements listed on their websites. If the Competent Authority is known the manufacturer is encouraged to look at this as well.

Navigating your transition to the IVDR and MDR

The Medical Devices Regulation (MDR) (EU) 2017/745 has a transition period of four years starting from May 2017, after which the Regulation now applies. The In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746 entered into force on the 25 May 2017 marking the start of a five-year transition period.

Manufacturers have the duration of the transition periods to update their Technical Documentation and processes to meet the new requirements if they want to place medical devices and in vitro diagnostic medical devices on the market in the European Union.

The MDR brings with it more scrutiny of Technical Documentation, addressing concerns over the assessment of product safety and performance by placing stricter requirements on clinical evaluation and post-market clinical follow-up. The IVDR brings with it significant changes to the regulatory requirements for IVD medical device manufacturers and introduces a new rule-based classification system with stricter notified body oversight, as well as significant changes to the depth and requirements of the associated Technical Documentation.

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Our Technical Documentation Review services deliver the efficiency you need to be both competitive in the market and maintain confidence through our robust technical reviews.

Standard

Our standard service reviews are completed by experienced BSI Product Experts, giving you confidence in the review.

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This service allows you to schedule your Technical Documentation review with a dedicated BSI Product Expert.

Five steps to CE or UKCA marking your product

Step 1

BSI prepares a quotation

A BSI representative meets with your organization to discuss your needs and the available solutions. We will also discuss the best service for your requirements.

Step 2

BSI performs a conformity assessment

A dedicated BSI scheme manager will be assigned to you, supporting your organization throughout the process. A QMS audit will then be performed and Technical Documentation reviewed by one of our experienced technical experts.

Step 3

Certification decision

Successful assessment leads to your BSI scheme manager recommending certification of your product. The BSI Certificate Decision Maker will then review the recommendation and, if satisfactory, approve certification.

Step 4

Issue certificate

Upon successful certification, you will be issued with a certificate. You will then be able to CE or UKCA mark your product and launch to market.

Step 5

Certification maintenance

On-going surveillance audits and reviews are required to monitor for continued compliance. Your BSI scheme manager will be able to support you with any queries you might have.

Talk to BSI today

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