Medical Devices with Ancillary Medicinal Substance

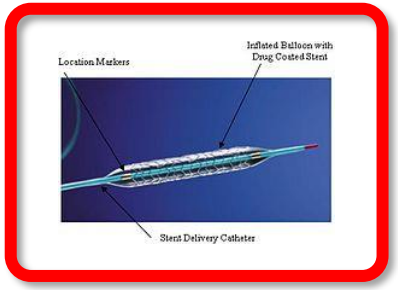
An overview of the MDR requirements and practical considerations

Theresa Jeary
Medicinal Expert, BSI
08 September 2021

AGENDA

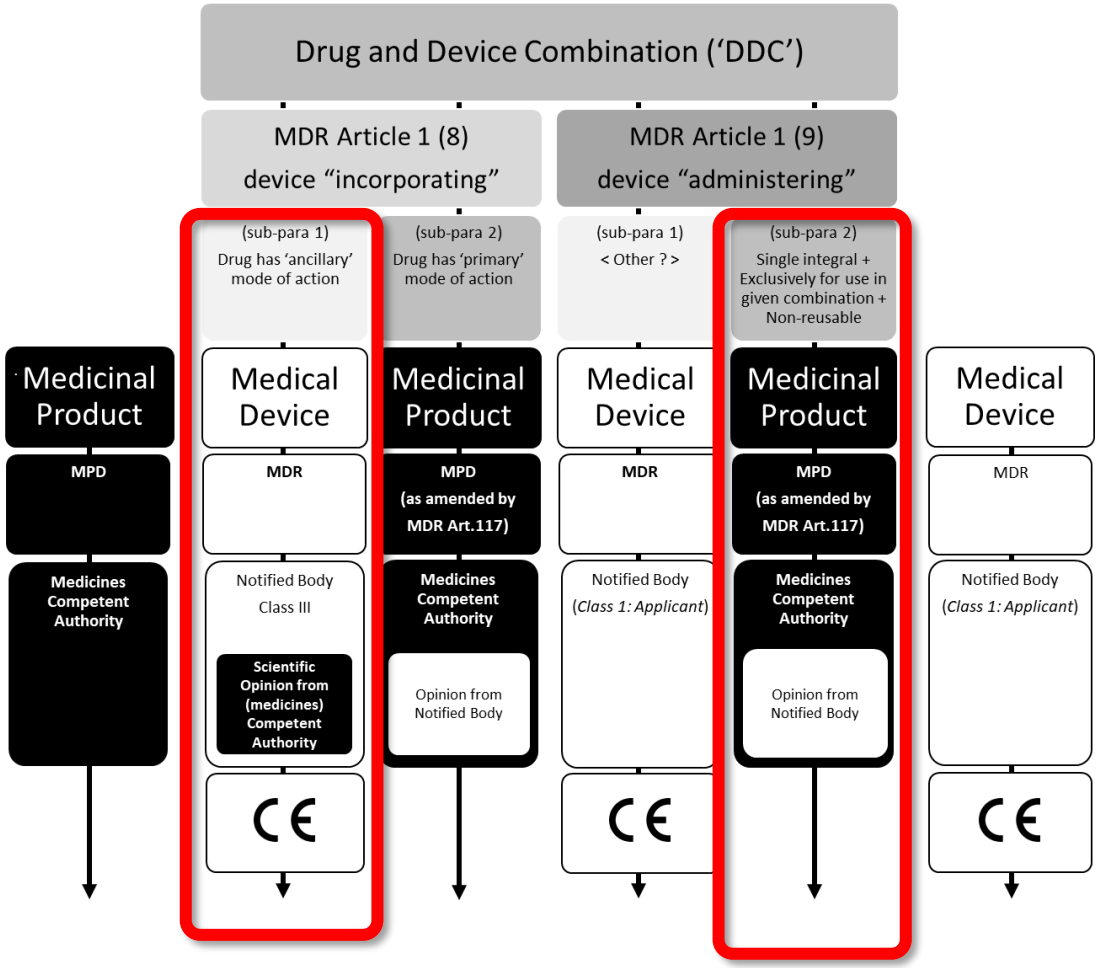
- Device and Drug Combinations in EU
- Introduction to BSI Medicinal team
- MDR Rule 14
- MDCG 2020-12 - MDR Conformity Assessment Process
- Competent Authority Assessment & Documentation Requirements
- EU Competent Authorities & Brexit Impacts

Legislation of combinations under the MDR



Single integral

Medicinal substance acts with ancillary action to the device



Single integral

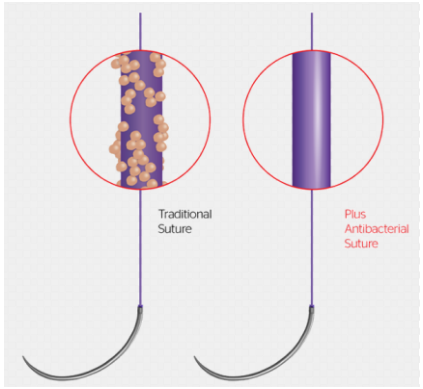
Intended exclusively for use in the given combination

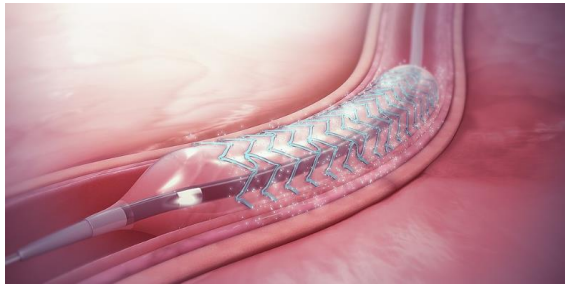
Non-reusable

Acknowledgements to Mark Chipperfield, of Corvus Device

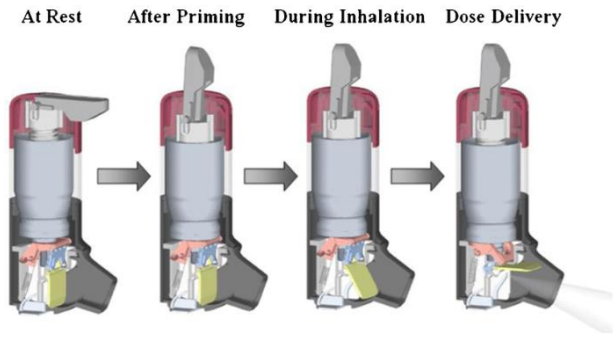
Device-Drug combination

Devices containing an integral ancillary medicinal substance

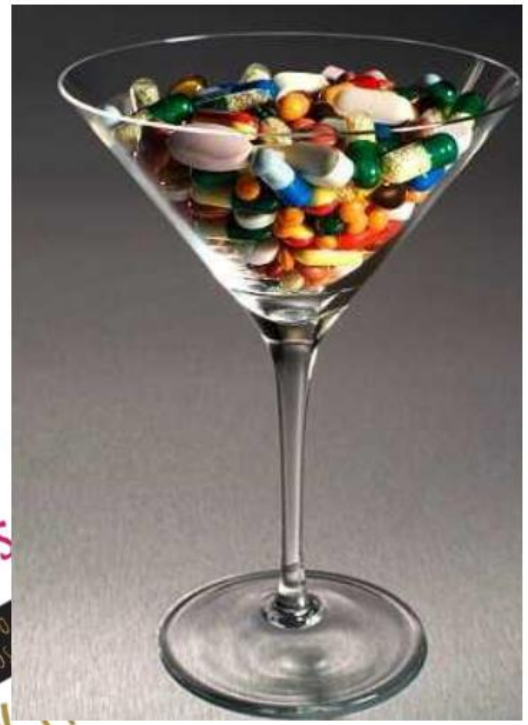


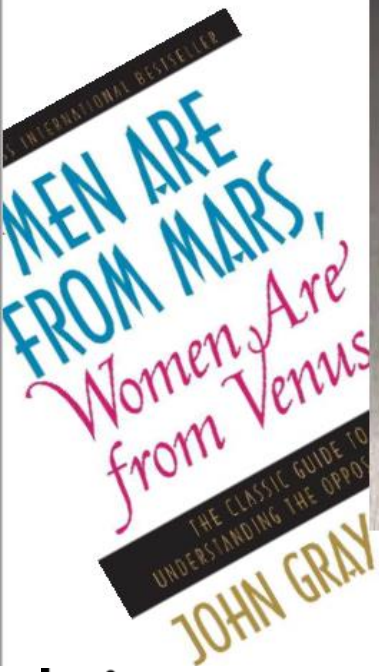


Drug-Device combination
Action of the medicine is principal



MEDICINES ARE FROM MARS





Devices Are from Venus

Acknowledgments: John Wilkinson, GMDN, 2020 Topra Symposium

Combinations = Legislation overlap

- Legislation governing medical devices is different to that for medicinal products
- **Requires involvement of appropriate expertise in the process**

Introduction to the Medicinal Team at BSI

Susanne Fornero

Jonathan Sutch

Arabe Ahmed

Godwill Iheagwaram

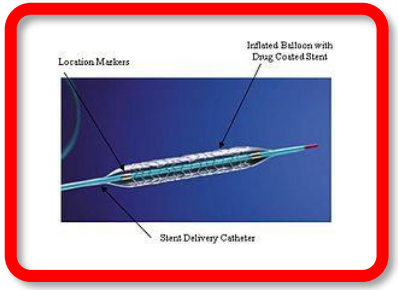
Theresa Jeary

Over 75 years combines experience and medicinal product expertise

- Drug & medicinal product development
- Biotechnology product expertise
- Good Manufacturing Procedures (GMPs)
- Development of medical devices with ancillary medicinal substances
- Regulatory submissions for medicinal product Marketing Authorisations
- Medicinal Consultations for devices with ancillary medicinal substances

Email: medicinal@bsigroup.com

Focus of todays webinar



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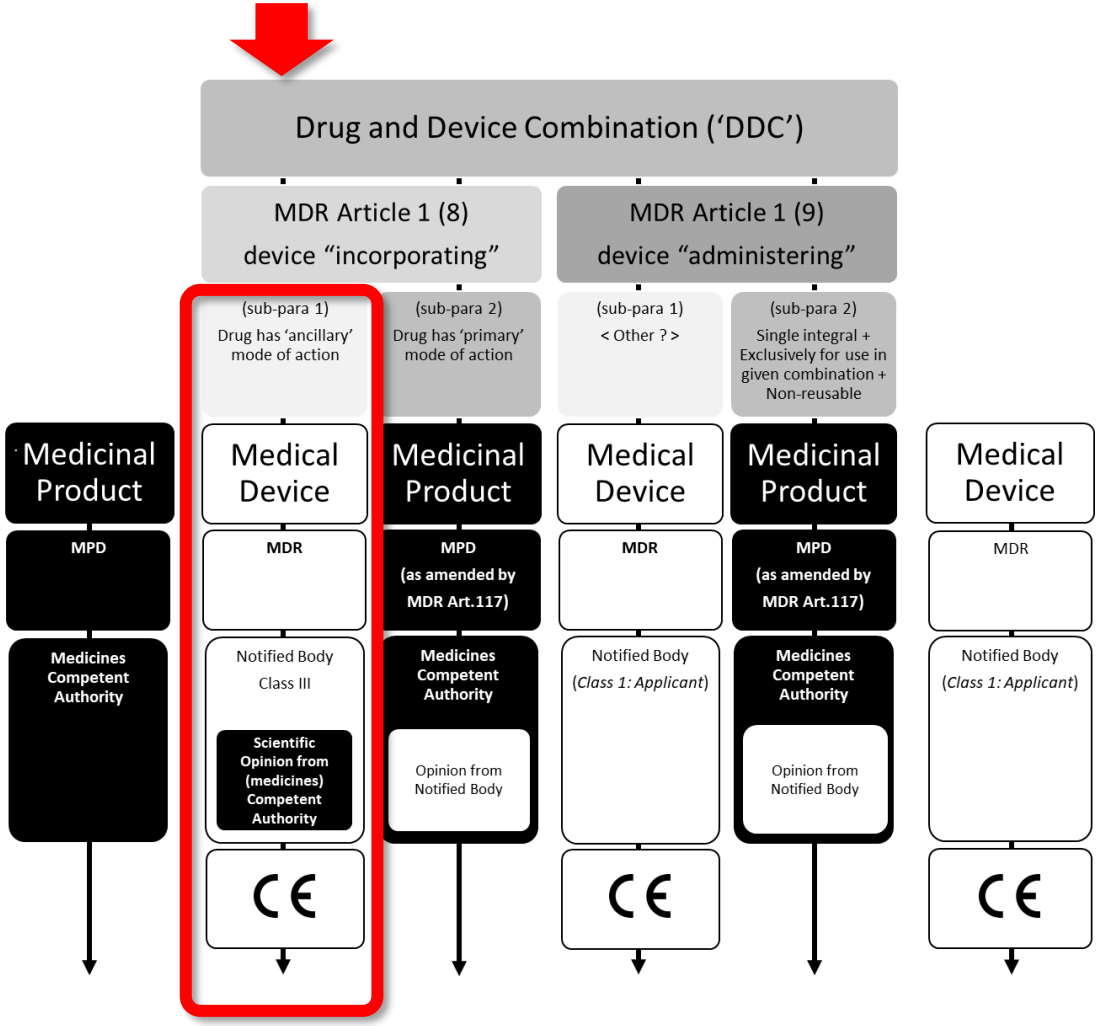


MDR Rule 14

MDR Change to applicable Rule

MDD Annex IX – Rule 13

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III.

All devices incorporating, as an integral part, a human blood derivative are in Class III

MDR Annex VIII – Rule 14

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma, as defined in point 10 of that directive, and that has action ancillary to that of the devices, are classified as Class III

MDCG 2020-12 Liability to act

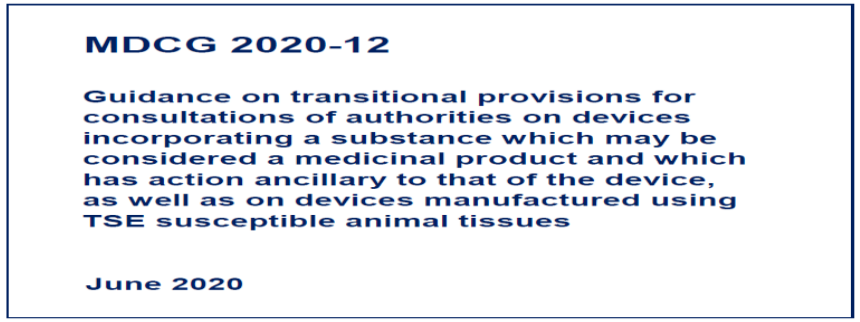
Note on "liability to act upon the body"

It should be noted that Annex I 7.4 of the MDD refers to devices in which the substance is **liable to act upon the body**. In the MDR (Article 52(9), referring to Article 1(8), and Section 5.2 of Annex IX), this is no longer the case. Therefore, for all those devices where the "liability to act upon the body" was used by the manufacturer as a justification not to follow the consultation, the consultation must take place under the MDR. In those cases where there are doubts on the applicability of the consultation, independently of any considerations concerning the classification of the device, the notified body should seek the scientific opinion as described in Annex IX Section 5.2 (b) of the MDR.

Borderline and Classification Guidance MDCG Group

Classification of medical devices

Borderline with medicinal products including general guidance, definitions of pharmacological,, immunological and metabolic means of action and diagnosis



Important Considerations

- If your device was exempt from Rule 13 under the MDD based on an agreed "liability to act" justification, Rule 14 of MDR is likely to apply with a medicines Consultation required
- Need to consider
  - If used separately can the substance be considered a medicinal product (Article 1 definition 2001/83/EC)
  - Does it have a pharmacological, metabolic. Immunological action?
  - Does the substance contribute to the claims made for the device , i.e. does it have an ancillary action?
  - Responsibility to classify device is the Manufacturers
  - NB verify clarification as part of application process
  - Disputes may occur & result in MDR Article 51 procedure

Are your devices impacted by the removal of "liability to act" sentence ?

a. Yes
b. No
c. Don't know

MDCG 2020-12 & MDR Conformity Assessment Process for Rule 14 Devices

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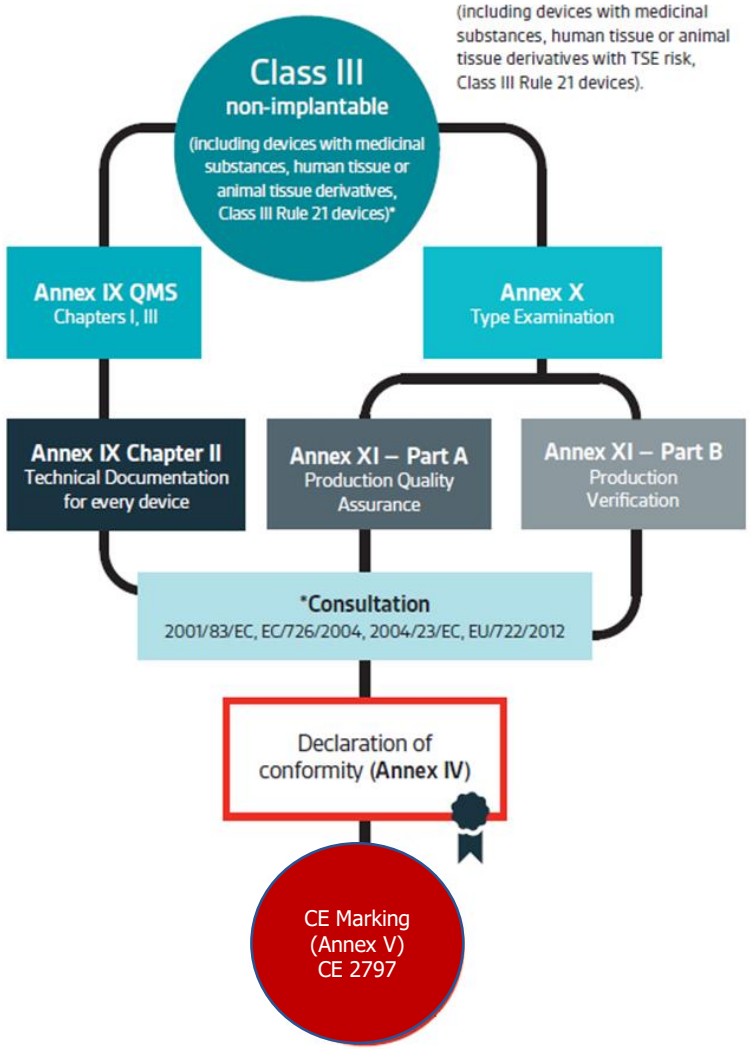
MDR Conformity Assessment Process

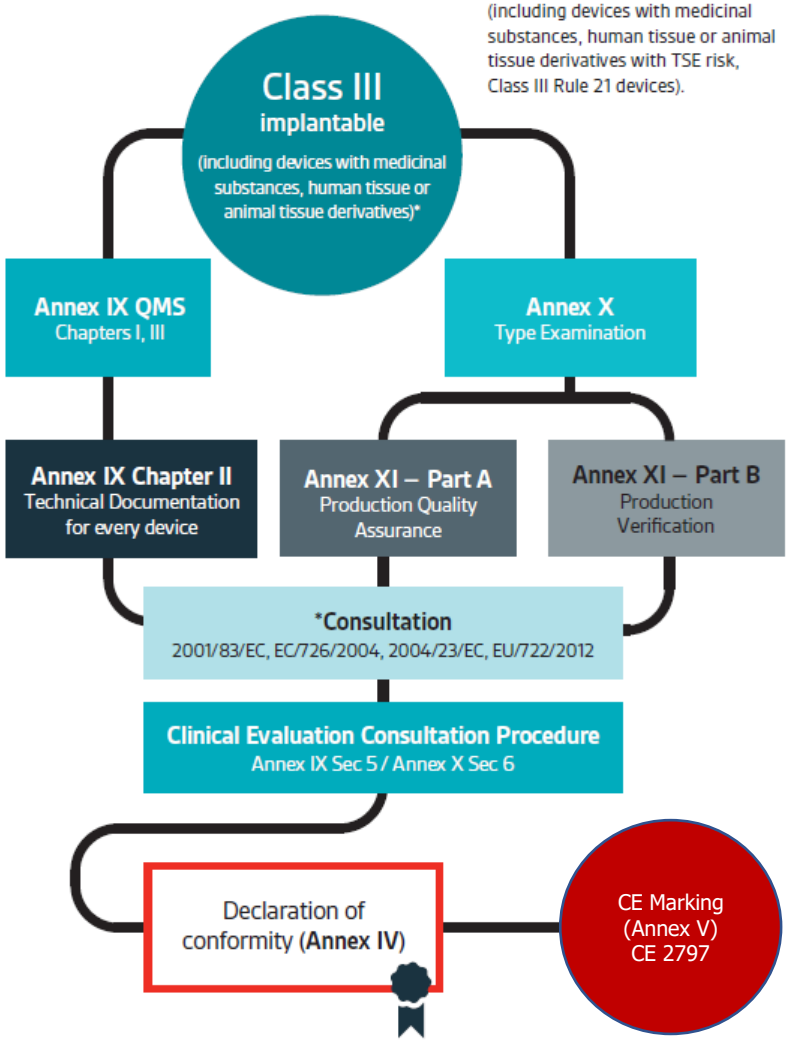
- NB examination of Design Dossier to confirm product conforms to relevant provisions of Regulation (GSPRs)
  - NB will verify that manufacturer has followed his declared procedures and those required by the Regulation
  - NB monitors the manufacturer's system for producing his Declaration of Conformity
- NB must seek opinion on medicinal aspects via Consultation process with a EU Competent Authority or EMA (Annex I, GSPR 12.1)

Routes to Conformity for Class III, Rule 14 Devices

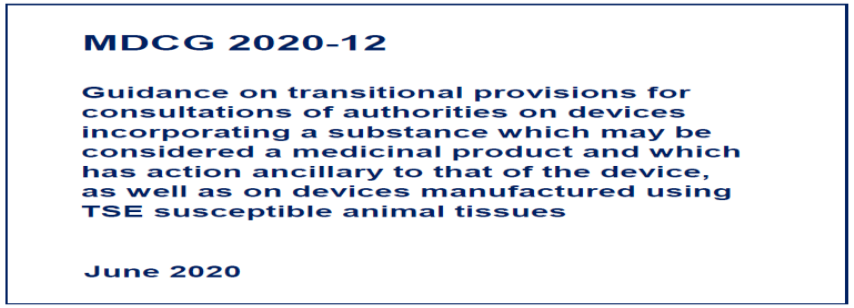
Class III non-implantable devices



Class III Implantable devices



MDCG 2020-12


MDCG 2020-12

Guidance on transitional provisions for consultations of authorities on devices incorporating a substance which may be considered a medicinal product and which has action ancillary to that of the device, as well as on devices manufactured using TSE susceptible animal tissues

June 2020

Confirms requirement for a consultation with a medicinal product authority as per Article 52 (9) of the MDR

NB is required to submit the full documentation package, including the last opinion under MDD /AIMD and a consolidated list of changes

NB can approach any medicinal products authority, is not required to be the agency consulted for MDD/AIMD

At the discretion of the medicines

CA to issue its opinion in less than 210 days

List of Changes ?

The ancillary substance

Its manufacturing process

The way the substance is incorporated into the device

Design, manufacturing of the device which could influence to quality, safety or usefulness of the ancillary substance

Medicinal consultation process and documentation requirements

Medicines Competent Authority Consultation

(b) Before issuing an EU technical documentation assessment certificate, the notified body shall, having verified the usefulness of the substance as part of the device and taking account of the intended purpose of the device, 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, either of which to be referred to in this Section as 'the medicinal products authority consulted' depending on which has been consulted under this point, on the quality and safety of the substance including the benefit or risk of the incorporation of the substance into the device. Where the device incorporates a human blood or plasma derivative or a substance that, if used separately, may be considered to be a medicinal product falling exclusively within the scope of the Annex to Regulation (EC) No 726/2004, the notified body shall seek the opinion of the EMA.

- Medicines Competent Authority assessment of the quality, safety and usefulness of the ancillary substance in the device
- CA Assessment Team comprised of Quality, Non-Clinical & Clinical Assessors
- BSI Medicinal Team write 'usefulness report', review medicinal dossier from manufacturer to ensure completeness and make application
- Competent Authority has a documentation validation step prior to review start
- Competent Authorities review the dossier following medicinal products procedures & timelines
- If questions are raised the procedure clock is stopped

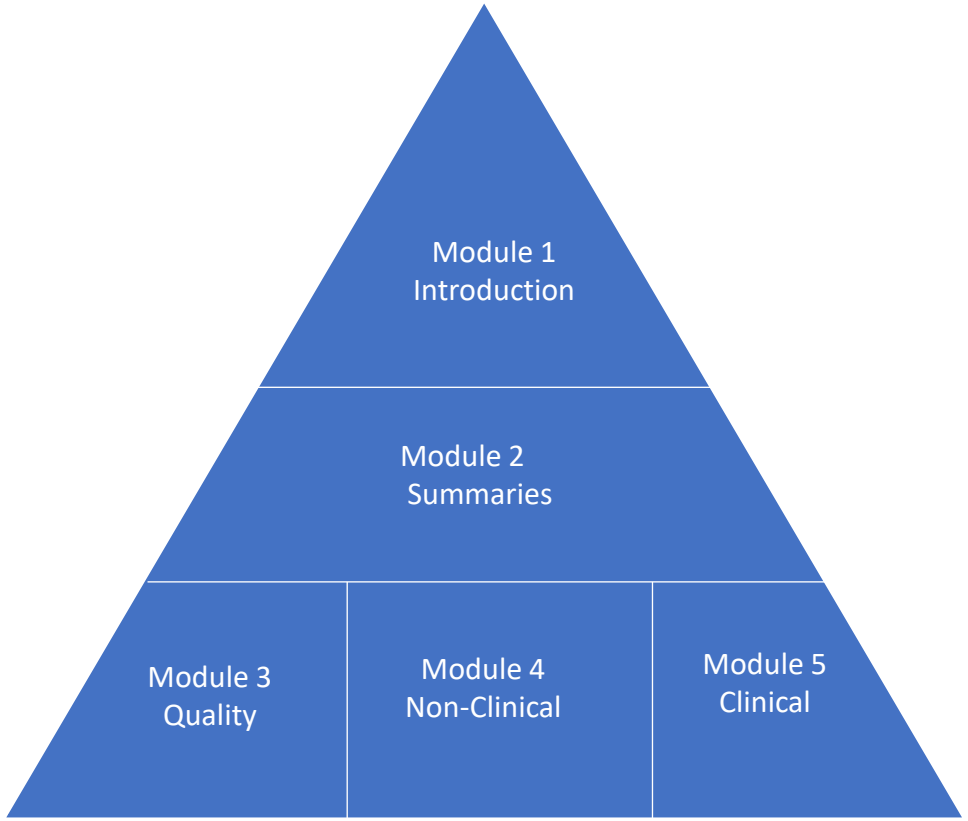
What is a usefulness assessment ?

The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action, and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.

Format of the Medicinal Dossier

- Stand-alone Dossier in Common Technical Document (CTD) format containing
  - Module 1: Introduction
  - Module 2: Summaries
  - Module 3: Quality Documentation
  - Module 4: Non-Clinical Data
  - Module 5: Clinical Data

Format of the Medicinal Dossier



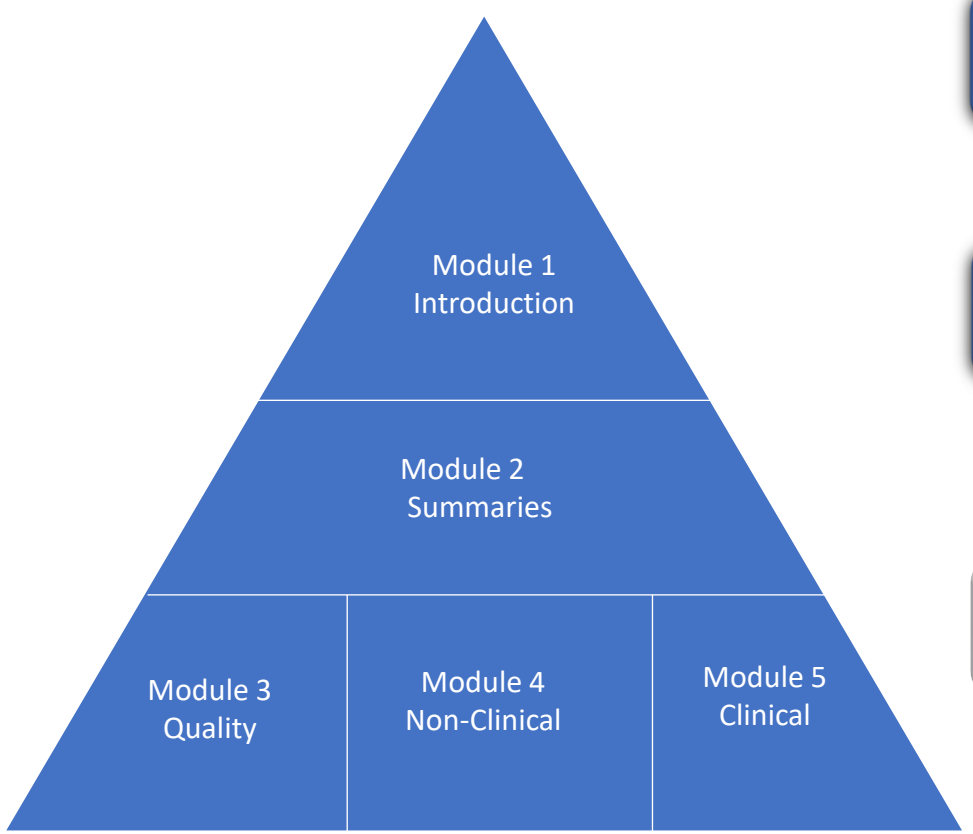
Module 1 : Introduction

- General description of the device
- Justification for the ancillary medicinal substance
- Critical evaluation of the results of the risk assessment
- GMP Declaration for the ancillary medicinal substance
- Labelling & IFU

Module 2: Summaries

- Expert Summaries
  - Quality Summary
  - Non Clinical Summary
  - Clinical Summary

Format of the Medicinal Dossier



Module 3: Quality

- Quality of the ancillary medicinal substance
- Quality of the incorporation of the medicinal substance in the device

Module 4: Non-clinical

- Relevant literature and pre-clinical testing related to the ancillary medicinal substance
- Non-clinical safety date, including pharmacodynamics, pharmacokinetics, local tolerance and toxicology

Module 5: Clinical

- Data to demonstrate and support the benefit-risk of the ancillary medicinal substance in the device
- Data to substantiate usefulness of the inclusion of the ancillary substance

Guidance on the format of the Medicinal Dossier

- MEDDEV 2.1/3 rev 3
- EMA dossier requirements
- Eudralex Notice to Applicants Volume 2B

EUROPEAN COMMISSION
DG ENTERPRISE and INDUSTRY
Directorate F, Unit F3 "Cosmetics and medical devices"

MEDICAL DEVICES: Guidance document

Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

MEDDEV 2. 1/3 rev 3

GUIDELINES RELATING TO THE APPLICATION OF:
THE COUNCIL DIRECTIVE 90/385/EEC ON ACTIVE IMPLANTABLE MEDICAL DEVICES
THE COUNCIL DIRECTIVE 93/42/EEC ON MEDICAL DEVICES

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 November 2019
EMA/CHMP/578661/2010 rev .1
Committee for Medicinal Products for Human Use (CHMP)

European Medicines Agency recommendation on the procedural aspects and dossier requirements for the consultation of the European Medicines Agency by a notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device or active implantable medical device

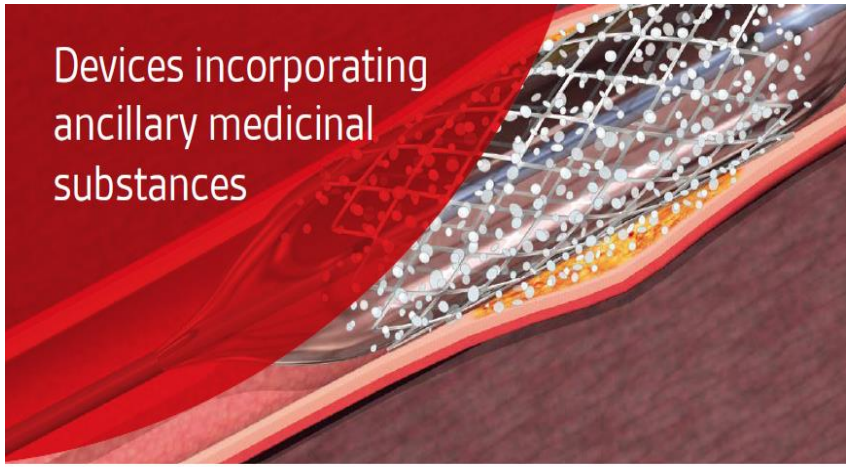
Volume 2B

Notice to Applicants

Medicinal products for human use

Presentation and format of the dossier

Common Technical Document (CTD)



Medicinal dossier guidance

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

EU Medicines Competent Authorities & Brexit Impacts

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EU Medicines Competent Authorities

The NB can choose any EU medicines CA for the consultation, apart from human blood derivatives and some chemical molecules which must be reviewed by EMA

Limited number who are willing to conduct such assessments for NBs at the present time

Prioritisation of Covid -19 Work has impacted timelines

Federal Institute for Drugs and Medical Devices

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

ansm
Agence nationale de sécurité du médicament et des produits de santé

OGYÉI National Institute of Pharmacy and Nutrition

SÚKL
State Institute for Drug Control

CBG MEB
MEDICINES EVALUATION BOARD

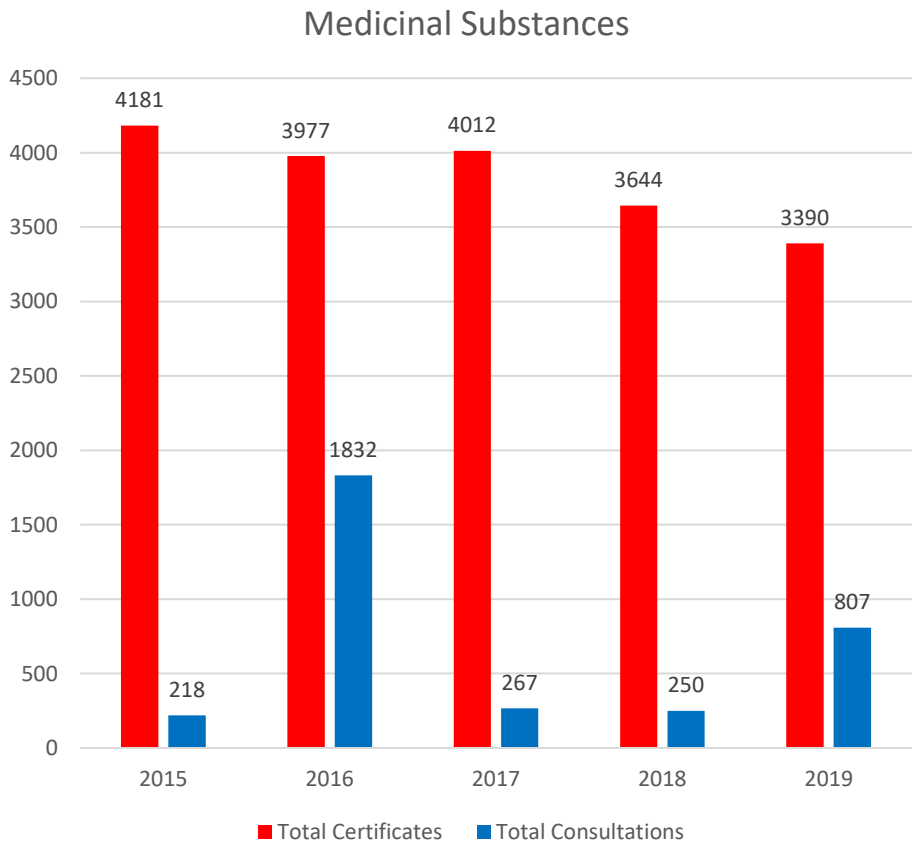
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Impacts of Brexit

- Under MDD, MHRA conducted over 70% of medicinal consultations for all NBs
- Transfers of MHRA Consultations are taken into consideration and acceptable as part of MDR re-consultation process
- UKCA applications for devices with ancillary medicinal substances require a consultation with MHRA

UK CA

Team–NB
Projected requirement for medicinal consultations



- Data from Team-NB (~26 NBs)
- Red = certificates under Rule 13
- Blue = consultation procedures
- Knowns:
  - Considerable extra burden for medicinal authorities
  - Risk to EU patients that devices disappear from the market
- Unknowns
  - Exact number of certificates and products that manufacturers will transfer to MDR
  - Which certificates expire when during the grace period (e.g. 2021, 2022, 2023 or 2024)
- Team-NB have raised their concerns to the HMA

Medicines Re-Consultation Process

Medicines CAs are reassessing the medicinal dossier and will ask questions

To provide visibility to CAs we require at least 6 months notice of submission

The CA has up to 210 days to issue an opinion and procedure clock is stopped when questions are raised

Try to avoid making significant changes for MDR Applications

When do you plan to make application for your device containing an ancillary medicinal substance ?

a. Documentation submitted and process underway
b. Within the next 6 months
c. I have a MDD Certificate until May 2024, so I have plenty of time

Summary

- Check the impact of Rule 14 on your device classification
- We need to notify the Medicines CA at least 6 months in advance of a submission
- The process could take 18 months to 2 years to complete
- Ensure your documentation meets the CA expectations and contains all relevant information and references
- Have realistic expectations for the process
- The conduct of an expedited assessment is at the discretion of the CA

Please share your MDR Application Plans with us ASAP

It is important that senior management understands the timelines associated with the MDR Re-Consultation process to allow them plan for the transition and ensure cooperation to resolve any CA questions that arise

The Medicinal Team will be actively providing updates and are here to support you through the process

BSI Medical Devices – Use Our Resources

https://www.bsigroup.com/en-GB/medical-devices/resources

Brochures, Guides and Documents

MDR guidance

MDD Best Practice Guidelines >
MDR Best Practice Guidelines >
MDR Mapping Guide >
MedDev 2.7.1 Rev 4 changes >
MDR Conformity Routes >
MDR Readiness Review >

Webinars

MDR Conformity Assessment Routes webinar

MDR - What we know

Download the presentation >

White Papers and Articles

Person responsible for regulatory compliance (PRRC) - MDR/IVDR Article 15

With the MDR and IVDR, European regulators aim to ensure companies have a regulatory expert – a Person Responsible for Regulatory Compliance (PRRC) – at their disposal, to ensure that the company is meeting certain specific EU requirements.

Software as a medical device - A comparison of the EU's approach with the US's approach

The International Medical Device Regulators Forum (IMDRF) aims to accelerate international medical device regulatory convergence. Through the IMDRF, regulators reached consensus on what software is considered a medical device. Regulators call it 'software as a medical device' (SaMD). This paper provides a comparison of how SaMD is regulated in the US and in the EU.

Machine learning AI in medical devices

How is AI different from traditional medical devices and medical software and what are the implications of those differences? What controls are necessary to ensure AI in healthcare is safe and effective?

Medical device clinical investigations – What's new under the MDR?

The conduct of a clinical investigation is one of the most time consuming and resource intensive activities that a medical device manufacturer can face. This paper discusses important new requirements for pre-market and post-market clinical investigations under the European MDR.

Training Resources

Medical devices regulation (MDR)	
Transition from MDD to MDR	1 day
Technical Documentation for CE - Marking	1 day
Requirements of MDR for CE - Marking	1 day
Implementing of MDR for CE- Marking	3 days

Further courses for medical devices manifacturers	
Medical Device Single Audit Program (MDSAP)	2 days
ISO 14971 Risk Management	1 day
Creating and Maintaining Technical Files	1 day
Post-market Surveillance and Vigilance	1 day
Clinical Evaluation for Medical Devices	1 day
Process Validation for the Medical Device Industry	1 day
Introduction to Medical Device Software	1 day

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https://www.linkedin.com/showcase/bsi-medical-devices/

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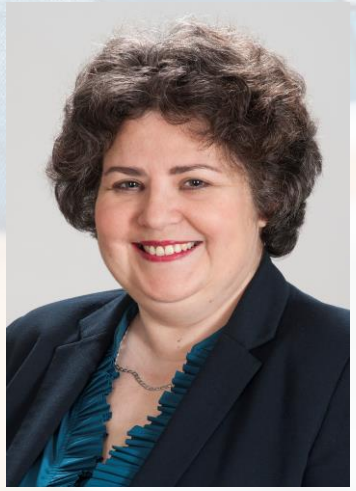
Questions?

Thank you for joining today

Theresa Jeary



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