EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Interface between medicinal product and medical devices development - Update on EMA implementation of the new medical devices legislation

Combined medicines and devices developments

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Overview

- Current State - regulatory framework in EU for medicinal products and medical devices
  - Regulatory interface - borderline and combination products
  - EMA role for combination products
  - Experience with MAAs of combination products
- Future State
  - Main changes introduced by Medical Device Regulations
  - EMA's role in medicine-medical device combinations
  - Implementation of the Medical Device Regulations
  - EMA support and advice for manufacturers

Interface between medicinal product and medical devices development

Medical device*

Any instrument, apparatus, appliance, material, software, or other article […], alone or in combination, intended by the manufacturer to be used in humans for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury/handicap
- investigation, replacement, modification of the anatomy; control of conception

➢ and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

*Council Directive 90/385/EEC and 93/42/EEC

Medicinal product#

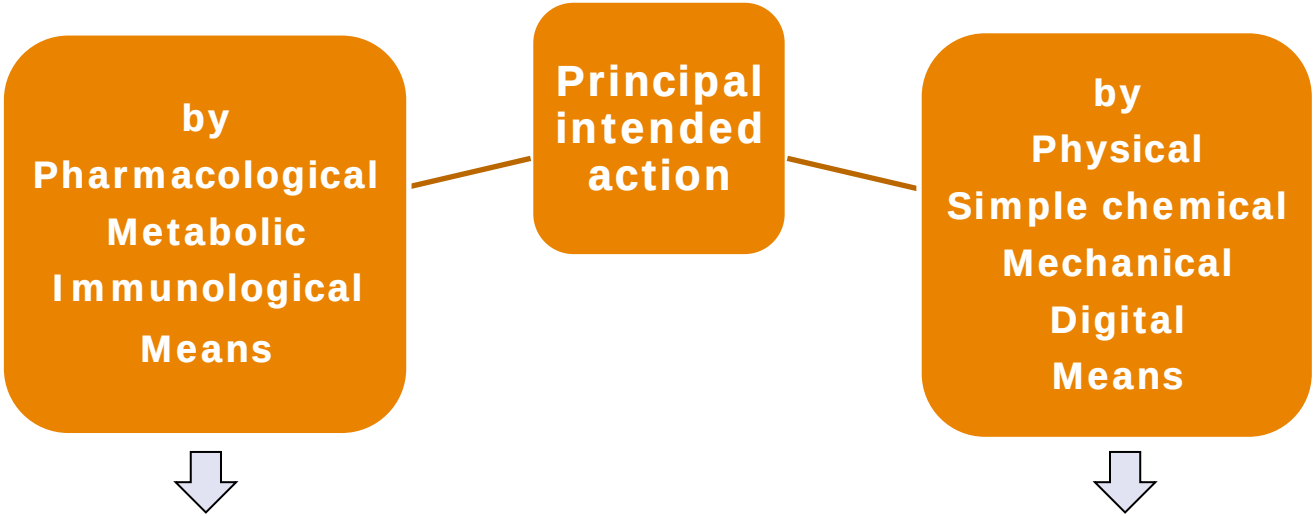
Any substance or combination of substances:

- having properties for treating or preventing disease in human beings or;
- may be used in or administered to human beings with view to restore, correct, modify physiological function

➢ by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

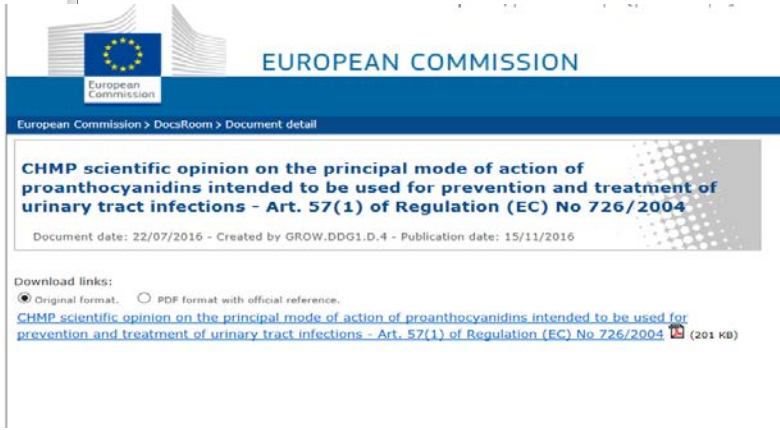
*Directive 2001/83/EC

Regulatory route for products in the interface



EMA experience with borderline discussions

The Commission decision stated that the group of products whose **principal intended action**, depending on proanthocyanidins (PAC) present in cranberry extract, is to prevent or treat cystitis, are not medical devices within the meaning of Article 1 (2) (a) of the Medical Devices Directive.



The legal basis […] is Article 13 (1) (d) of the Medical Devices Directive […] This Article allows the Commission to take a decision, at the request of an EU country, on whether a product or product group falls within the definition of a 'medical device' according to Article 1 (2) (d) of the Medical Devices Directive.

EMA's current role in review of medicinal product and medical device combinations

Medicinal products with medical device component

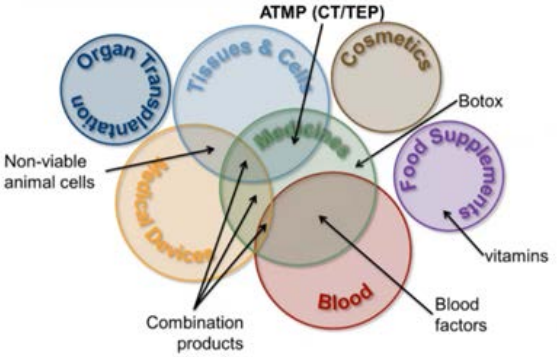
- Integral: single integral product; not reusable, intended exclusively for use with medicinal product (No CE-mark required)
- Non-integral (CE mark required prior to CHMP opinion)

ATMP combination products

- One or more medical devices as an integral part of the medicine
- Existing procedural advice on the consultation of Notified Bodies

Medical devices incorporating (ancillary) medicinal substances

- Consultation of NB with NCA/EMA
- Established procedure and guidance for initial and post-consultation (210 days)



Medicinal product with Integral device component

Where the device and medicinal product…

- **form a single integral product**
- **are exclusively for use in the given combination**
- **not reusable**

Examples:

- Single-entity combination products, such as a pre-filled syringes and inhalers
- Fibrinogen and thrombin coated matrix (sponge)

Medicinal product with Non-Integral device component

Where the device and the medicinal product are separate items but intended for use together

- Can be **Co-packaged** or **Sold separately**

Examples:

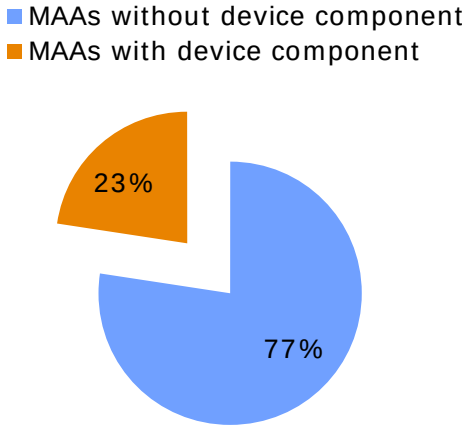
- Insulin cartridges to be used with reusable pen
- Tablet delivery system with controller for pain management

Experience with initial MAAs since January 2010

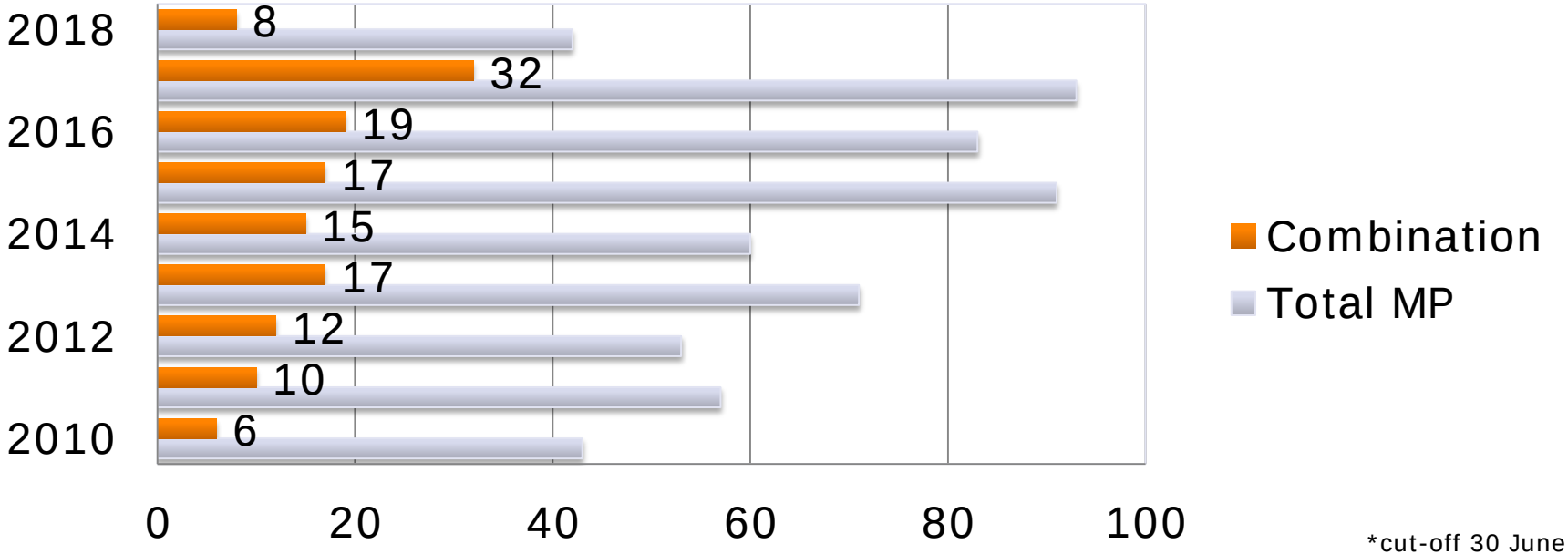
- MAAs approved since Jan 2010 (and still valid) with a cut-off 30 June 2018 were reviewed for medical device components (integral or non-integral)
- Following results are work in progress

Experience with initial MAAs since January 2010

- 593 initial MAAs approved from Jan 2010 to June 2018*
  (*still on market and not suspended)
- Majority of medical devices:
  - ✓ pre-filled syringes / pre-filled pens (eg diabetes)
  - ✓ inhalers (COPD/Asthma)
- Nasal sprays; with metered pump
- Tablet delivery system with controller for pain management
- ATMPs (e.g. autologous cultured chondrocytes embedded in a biodegradable matrix or scaffold)

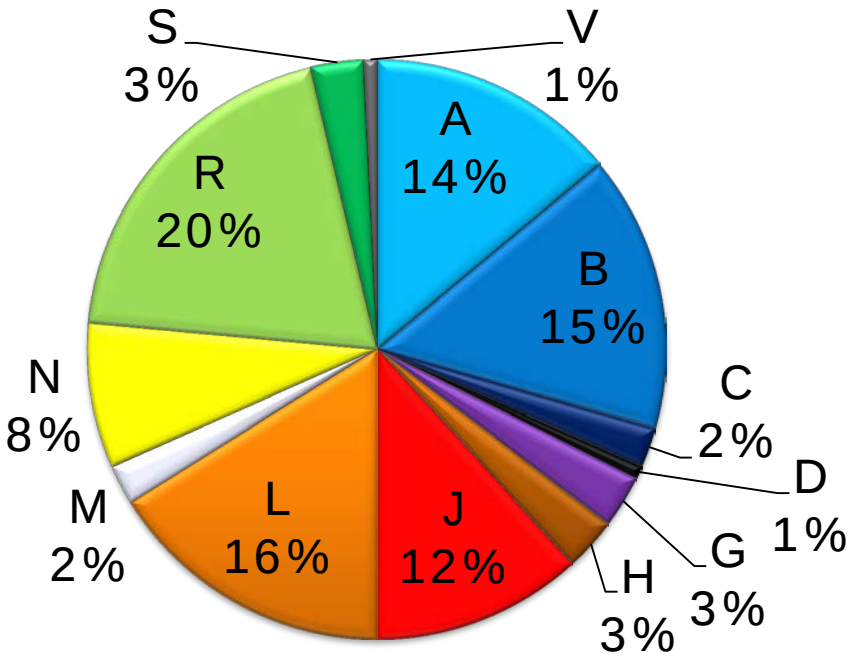


Medicinal product - medical device combinations approved with valid MA*



*cut-off 30 June 2018

Therapeutic areas of medicinal product - medical device combinations



A=Alimentary tract and metabolism

B=Blood and blood forming organs

C=Cardiovascular system

D=Dermatologicals

G=Genito-urinary system

S=Systemic hormonal preparations

J=Anti-infectives

L=Antineoplastic and immunomodulating agents

M=Musculo-skeletal system

N=Nervous system

R=Respiratory system

S=Sensory organs

V=Various

Update on EMA implementation of the new medical devices legislation

New medical devices and in vitro diagnostics Regulations

Current device legislation

- Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) (1990)
- Council Directive 93/42/EEC on Medical Devices (MDD) (1993)
- Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDMD) (1998)

Two new Regulations entered into force on the 25th of May 2017

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR)
- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (IVDR)

- Full application for the MDR: **26 May 2020**
- Full application of the IVDR: **26 May 2022**

Main changes to the Medical Device legislation

- Strengthened governance structure and coordination
- Shift from pre-approval to life-cycle approach
- Definition of medical devices extended
- Stricter requirements and oversight of the Notified Bodies
- New processes for clinical investigations, vigilance and post-market surveillance
- New requirements for transparency and traceability (Eudamed, UDI)
- Harmonization efforts between Member States by introducing **Medical Device Coordination Group (MDCG)**
- **New role / responsibilities for EMA (NCAs)**

EMA's future role in review of medicinal product and medical device combinations

- Consultation on **borderline products** by EC
- Consultation on medical devices composed of ***substances or combinations of substances*** *that are absorbed by or locally dispersed in the human body)* by a NB **[NEW]**
- Consultation on **companion diagnostics** by a NB **[NEW]**
- Consultation on **MD incorporating an ancillary Medicinal Product** *(e.g. substances derived from human blood or human plasma, biotech products)* by a NB
- Marketing authorisation dossier for **Medicinal products with integral device component** *e.g. (pre-filled syringes)* to contain Declaration of conformity, CE cert or NB opinion ("MDR Article 117") **[NEW]**

EMA Implementation Workstreams

Borderline products

EC and Medical Device Coordination Group (MDCG) can consult EMA for devices on borderline with medicinal products

CHMP/CAT/HMPC scientific opinion on borderline products under Art. 57(1)

Medical devices composed of substances

Implement new consultation procedures

Building on consultation already in place for ancillary substances

Companion Diagnostics

Building on PGWP concept paper for predictive biomarker assay development

Implement new consultation procedures

Scientific and procedural guidance under development

MD incorporating an ancillary Medicinal Product

Update current procedures with references to new regulations

Updated external guidance to be released

Medicinal products with integral device component

QWP/BWP concept paper on quality requirements of drug device combinations

Q&A document on practical implementation under development

Nov 2017– EC and CAMD* implementation roadmap

https://www.camd-europe.eu/wp-content/uploads/2018/05/NEWS_171107_MDR-IVDR_RoadMap_v1.3-1.pdf

8 road map priority clusters

- Clinical Evaluation & Clinical investigation (MD); Performance Evaluation & Performance Studies (IVD)
- Scope & Classification
- Notified Bodies
- Post-Market Surveillance & Vigilance
- Eudamed & UDI
- Market Surveillance
- IVD specific issues
- Over-arching &Cross-cutting Priorities

- MDR/IVDR implementation task force to facilitate implementation within the medical devices network
- Practical guide for regulatory authorities and EC to work together towards implementation

- **EMA** specifically identified as **responsible party for CDx and combination products**
- **EMA** participation in EC working groups
- **EMA** engagement with device and medicines stakeholders

*CAMD=Competent Authorities for Medical Devices

Companion Diagnostics: New EU definition

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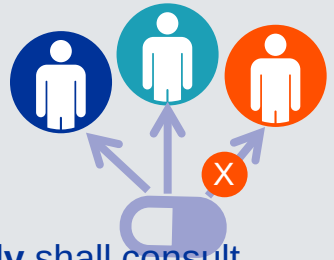
Art. 2(7) IVDR

"(7) 'companion diagnostic' means a device which is **essential for the safe and effective use** of corresponding medicinal product to: (a) **Identify**, before and/or during treatment, **patients** who are most likely to **benefit from the corresponding medicinal product**, or (b) **identify**, before and/or during treatment, **patients** likely to **be at increased risk of serious adverse reactions** as a result of treatment with the corresponding medicinal product."



IVDR Article 48(3)

For **companion diagnostics** the **notified body** shall consult the concerned **competent authority** designated in accordance with Directive 2001/83/EC or the European Medicines Agency (**EMA**), as applicable

ANNEX IX, Chapter II - 5.2.

The **notified body** shall, before issuing an **EU technical documentation assessment certificate** for the companion diagnostic and on the basis of the **draft summary of safety and performance** […] consult one of the competent authorities […] regarding the suitability of the device in relation to the medicinal product concerned.

Companion Diagnostics: New Consultation Procedure

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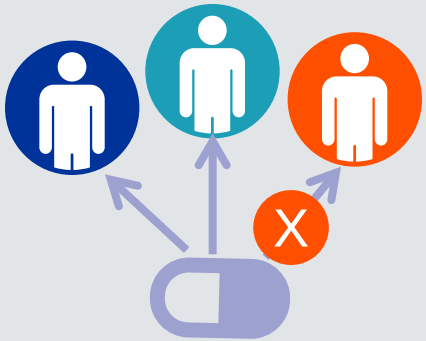


- **Consultation** when
  - the medicinal product **falls exclusively within the scope of the Annex** to Regulation (EC) No 726/2004, or
  - medicinal product concerned is **already authorised**, or
  - if an **application for its authorisation has been submitted**
- Regulation foresees **scientific opinion, within 60d** after receipt of valid documentation; may be **extended** once for a **further 60d** on justified grounds
- The opinion and any possible update to be **included in the documentation of the notified body concerning the device**
- Any **(post-approval) changes** requiring consultation, a scientific opinion should be provided **within 30 days after receipt of the valid documentation**

Changes for medicinal products with integral device - Article 117

Medical Device Regulation

Article 117 [Amendment to Directive 2001/83/EC, Annex I, point 12 of Section 3.2.]

Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*), a product is governed by this Directive [2001/83/EC], **the marketing authorisation dossier shall include,** where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU **declaration of conformity or the relevant certificate issued by a notified body** allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, **the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body** designated in accordance with that Regulation for the type of device in question.

Medicinal product with Integral device component

Current state:

- Regulated as medicinal product (Directive 2001/83/EC or Regulation726/2004)
- Relevant essential requirements in Annex I to devices directive (93/42/EEC) apply as far as safety and performance related features of the device are concerned.
- CE mark/certification not required

Future state:

- Regulated as medicinal product (Directive 2001/83/EC or Regulation726/2004)
- NEW Relevant **general safety and performance** requirements in Annex I to devices **Regulation (2017/745)** apply as far as safety and performance related features of the device are concerned.
- NEW **Article 117: Declaration of conformity** or **CE certificate** or **notified body opinion***

*Does not apply to Class I non-sterile and non-measuring device

ANNEX I Requirements

Medical Device Directive (MDD)

- Essential Requirements (ERs)
- 13 clauses (~94 individual requirements)

Medical Device Regulation (MDR)

- General Safety and Performance Requirements (GSPRs)
- 23 clauses (~178 individual requirements)

- Scope and topics consistent
- Align the GSPR with harmonized standards and existing guidance.
- Greatest impact of changes will be for medicinal substances and substances absorbed or locally dispersed; materials of biological origin; substances of concern, i.e. substances listed as being carcinogenic, mutagenic or endocrine disrupting; labelling; and cybersecurity.

Article 117 implementation

Guideline on 'Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product' (QWP and BWP)

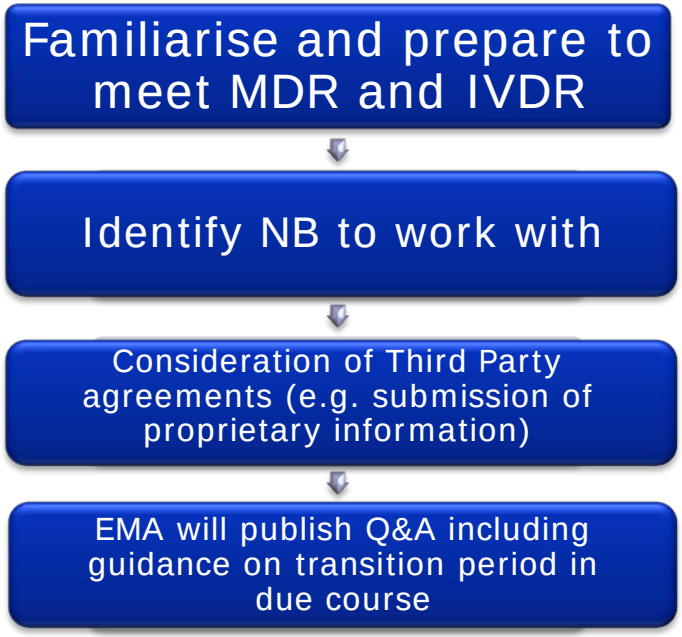
➔Scientific guideline

➔Main focus: dossier requirements for regulatory submissions (Module 3)

➔Informal discussions with Notified Bodies

- **Work ongoing to address the open questions**

Advice to manufacturers on preparing for the regulations



EMA support:

- **Regulatory and Scientific Advice**
  - Can be used at any stage of development – earlier the better!
- **EMA Innovation Task Force (ITF)**
- **ATMP classification procedures for combined ATMP** Regulation 1394/2007/EC

Any questions?

Further information

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