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SCIENCE MEDICINES HEALTH

EMA activities on medical devices

SME Info Day – 18 October 2024

Presented by Christelle Bouygues, Antonella Baron, Hilde Bastaerts, Stiina Aarum
Human Medicines Division, European Medicines Agency

Disclaimer

 The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties. The presenter does not have any conflict of interests.

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EMA roles and responsibilities for Medical Devices

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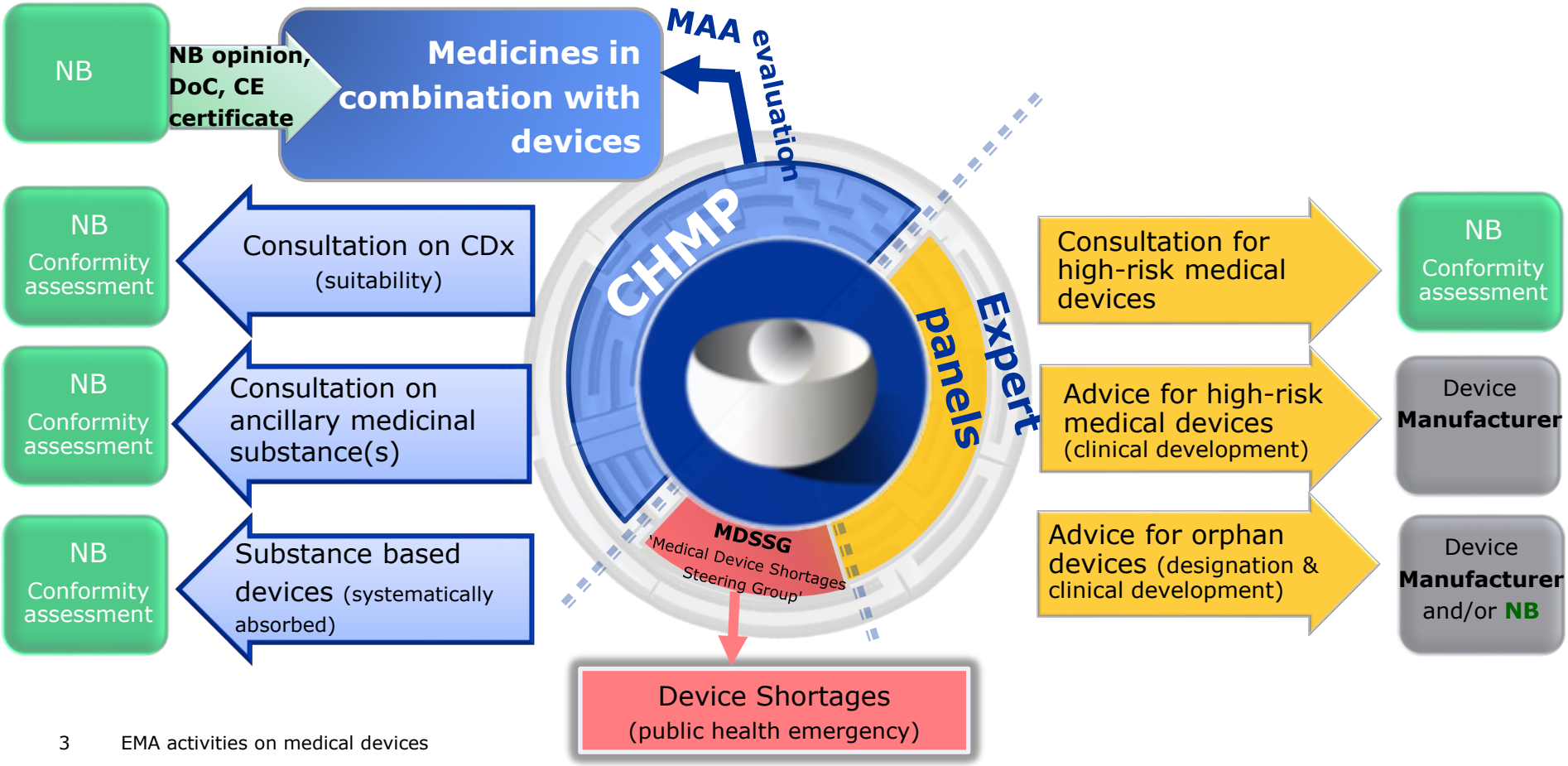

Medicines used in combination with medical devices

SME Info Day – 18 October 2024

Presented by Christelle Bouygues, Regulatory Affairs Office, Human Medicines Division, EMA

Interface medicines and devices frameworks

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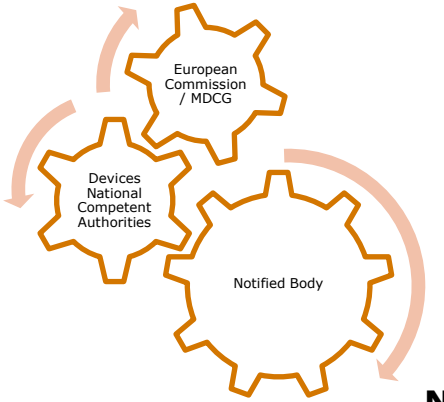
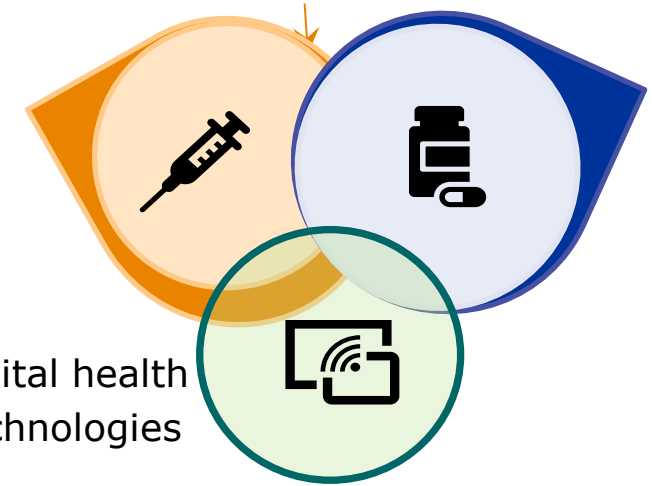
Medical device ((EU) 2017/745) / in vitro diagnostic ((EU) 2017/746) Regulations

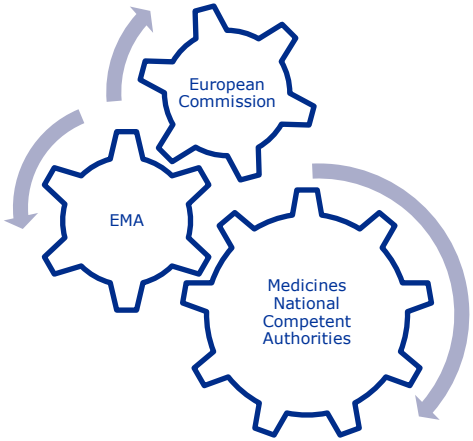


Combinations of Drug and Devices



Digital health technologies

Medicinal Product Directive (2001/83/EC)/ Regulation (EC)726/2004



Need to ascertain the applicable regulatory framework for a concerned product

- Is it a medicinal product vs a medical device?
- Is it a medical device vs a container closure system?
- Is it an integral vs co-packaged combination?

Combination type of a medicine used with a medical device

Notified Body involvement

Integral	(drug-device combination): Medicinal product and device forming : • a **single integral** product, and • **intended exclusively for** use in the given combination and, • is **not reusable** **At time of placing on the market**	**Regulated as MP (**The only combination defined in the MDR: Art 1(8) and Art 1(9)**)** **Art 117 MDR – compliance with GSPRs:** • **Notified Body opinion (NBop)** • **CE certificate or** • **Declaration of Conformity (DoC) (non-sterile non-measuring Class I devices only)**
Co-packaged	Medicinal product and medical device packaged **together in a single package**	**Regulated under MDR** • CE certificate or DoC
Referenced in PI	Medicinal product and medical **device packaged/supplied separately** but according to the labelling intended for use together	**Regulated under MDR / IVDR** • CE certificate or DoC

+ Device-specific aspects relevant to the Q,S,E of the medicine in the MAA (see DDC Quality guideline)

Role of EMA and National Competent Authorities (NCAs) vs Notified Bodies

CHMP guideline on drug-device combinations and core principles:

QWP-BWP Guideline on medicinal products used with a medical device (europa.eu)

- **EMA/NCAs** evaluate device-specific aspects relevant to quality, safety and efficacy of the medicinal product
- **Notified Bodies (NBs)** assess the relevant General Safety and Performance Requirements (GSPRs) for the medical device

Guideline objective: To minimise overlap between EMA/NCAs and Notified Body reviews

GSPR compliance check, content and review of an application for Notified Body Opinion (NBOp) fall outside EMA/NCA remit

MDR Article 117 – Experience and points for consideration for integral drug-device combination

- **NBOp expected to conclude on full compliance**
  - CHMP cannot follow-up on deficiencies identified in the NBOp
  - CHMP cannot bypass the NBOp conclusion
  - In case of partial GSPR compliance, the applicant should always liaise with the Notified Body to address the deficiencies and provide a revised NBOp before CHMP Opinion

- **NBOp expected to reflect the intended use**
  - Example: measuring function in the dossier not reflected in the NBOp

- **Device qualification and classification fall outside EMA legal remit**
  - Examples for prefilled syringes: Prefilled syringe without needle: I, Is, IIa?

Life cycle management of an integral device

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Guiding principle **when to provide a new / revised NBOp** for the device of an iDDC with a variation / extension :

1) new device
2) In case of major changes to an existing device, such as:
   - change to its design
   - Addition or replacement of an integral device (part)
   - change to its performance characteristics
   - change to its intended purpose – e.g. different patient population and/or new user (e.g. home versus hospital setting), new usability study, and/or significantly different instructions for use.

   which may have a significant impact on the delivery or the quality (e.g. to consider impact on Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs) and control strategy), safety, or efficacy of the medicinal product.
3) changes to the medicinal product which may impact the performance or safety of a device (e.g. new finished product formulation resulting in different viscosity significantly affecting device performance).

In case a new or revised **NBOp considered not needed**, applicants are expected **to provide a justification and risk assessment in Module 3.2.R.**

Reference documents

❑ Medical Device Regulation ((EU) 2017/745) - MDR

CL2017R0745EN0030010.0001.3bi_cp 1..1 (europa.eu)

❑ In Vitro Diagnostic Regulation ((EU) 2017/746) – IVDR

CL2017R0746EN0000030.0001_cp 1..1 (europa.eu)

❑ EMA/CMDh Q&A on the implementation of the MDR and IVDR (Update May 2024)

Questions & Answers on the implementation of the Regulations on medical devices and in vitro diagnostic medical devices (europa.eu)

❑ Revision of regulatory framework on variations (ongoing)

- ➢ To address the lack of granularity of the Classification guideline and the need to reflect the MDR requirements

Guidelines on the details of the various categories of variations 2013-C 223-01 _13 June 2024 - proposed revision - track changes (europa.eu) (public consultation closed)

Companion diagnostics (CDx)

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Companion Diagnostics: Overview of the IVDR Requirements and the EMA Consultation Process for CDx

Presented by Antonella Baron, Oncology and radiopharmaceuticals Office, Human Medicines Division, EMA

Biomarkers in Drug Development

- Precision Medicine is critical to many drug development programs

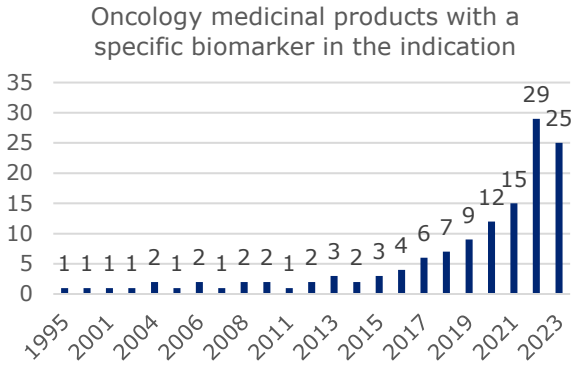
Dramatic increase in biomarker-targeted drug development programs in oncology.

- In the early 1990s, 5% of new drug approvals were for targeted therapies.
- More than a third of new drug approvals in oncology in the last 4 years are personalized medicine

OLD chemotherapy
Molecular targets unspecific or unknown
Low precision
Unspecific, massive collateral damage

→

YOUNG targeted medicines
Precise targeting of defined molecular targets (e.g. receptors, mutations)
High selectivity
High benefit-risk ratio



Biomarkers vs *In Vitro Diagnostics* (IVDs)

Biomarkers

A characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Types of biomarkers: Molecular, histologic, radiographic, or physiologic characteristics

In Vitro Diagnostic Test

Well-defined system used to measure a biomarker status in the patient population

System includes the specimen, the analyte, the instruments, the protocol and type of test and the clinical decision point, (i.e. clinical cut off) for the test system

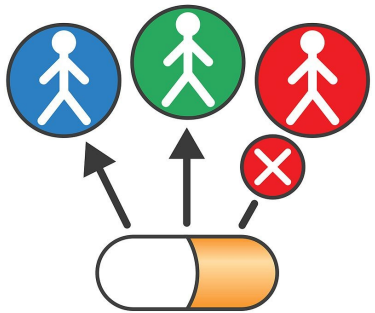
Biomarker: mutations D835 and I836 in fms-like tyrosin kinase 3 (FLT3) gene	LeukoStrat CDx FLT3 Mutation Assay

EU legal definition of Companion Diagnostic (CDx) - Art. 2(7) IVDR 2017/746

"(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."



The legal role of EMA in CDx regulation (26 May 2022)

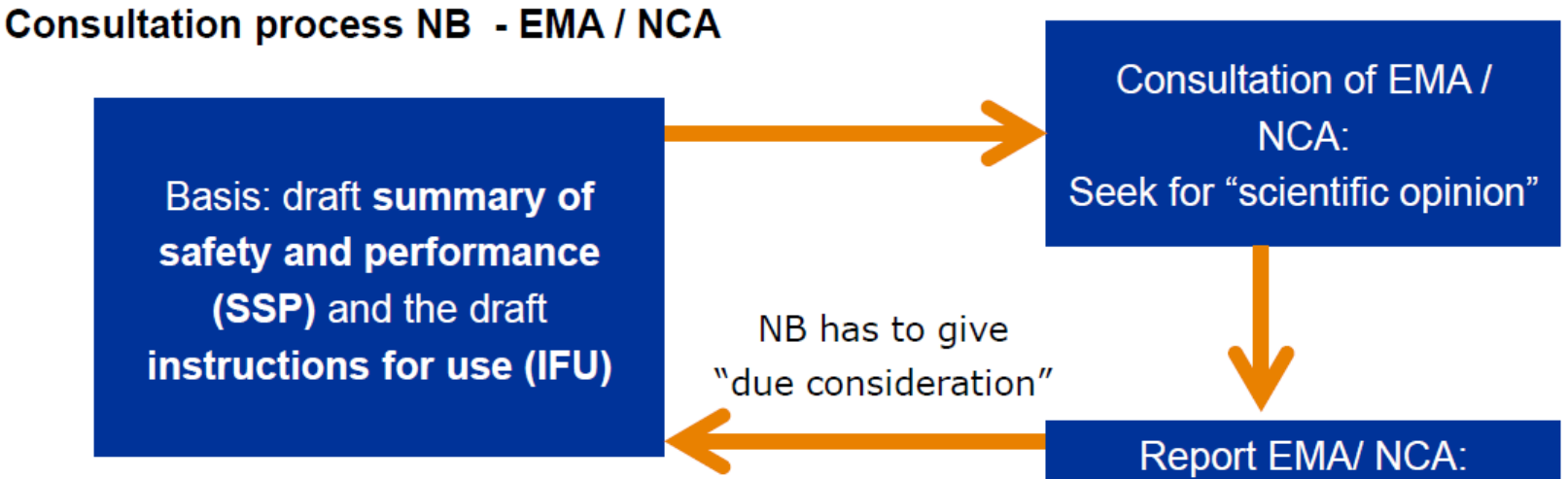
Conformity assessment - IVDR Article 48

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

SSP & IFU - 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 and the draft instructions for use** […] consult one of the competent authorities […] **regarding the suitability of the device in relation to the medicinal product concerned**.

Conformity assessment and scientific consultation



Please also refer to the MDCG 2022-9 - Summary of safety and performance template

Suitability of the CDx for use with the concerned medicinal product(s)

'Suitability' relates to the use of a CDx with (a) particular medicinal product(s), given the performance and use claimed by the manufacturer.

Aspects that are considered when assessing the suitability of a CDx:

- Scientific validity/rationale (the association of an analyte with a clinical condition or a physiological state)
- Analytical performance (the ability of a device to correctly detect or measure a particular analyte)
- Clinical performance

(the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user)

- Procedural timetables | European Medicines Agency (europa.eu)

This process is independent from the medicinal product Marketing Authorization Application

CHMP MAA D80 Clinical Assessment Report template insights

In vitro biomarker test for patient selection for efficacy/safety

Scientific rationale for the choice of the predictive in vitro biomarker test (e.g. **prevalence, relation to disease mechanism**).

Analytical method including **assay platform, specimen, pre-analytical processing requirements and read-out method**.

Analytical and clinical validation strategy:

- Analytical validity: For verifying the suitability of an assay, **robustness, accuracy, specificity, sensitivity and linearity** should be considered depending on the analytical platform
- Clinical validity (**sensitivity/specificity**) should be described either by correlation with a clinical endpoint (for novel assays) or –if available- by concordance study with a clinically valid reference assay
- **Cut-point selection** should be described and discussed in detail since it is of particular importance for the benefit /risk assessment.

Relevant guidance published on the EMA webpage

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- **Guidance on the procedural aspects** for the consultation to the EMA by a notified body on CDx
- **Assessment Report template** for consultation on CDx
- **Application forms** for initial and follow-up consultation on CDx
- **Letter of intent-template** for the submission of a consultation
- **Q&A** on practical arrangements on the CDx consultation procedure
- Scientific Advice

Medical devices | European Medicines Agency (europa.eu)

frequently-asked-questions-medicinal-products-development-and-assessment-involving-companion-diagnostic-cdx_en.pdf

Scientific advice and protocol assistance | European Medicines Agency (EMA) (europa.eu)

Take home messages

- Information on biomarker test should be included in the MAA following D80 Clinical Assessment Report template insights and frequently-asked-questions-medicinal-products-development-and-assessment-involving-companion-diagnostic-cdx_en.pdf
- For Companion Diagnostics (CDx), the EMA needs to be consulted by Notified Bodies on the suitability of the CDx for use with the medicine
- Assessment of suitability includes a review of scientific validity (rationale) and of the analytical and clinical performance of the CDx (evidence requirements are detailed on the EMA website https://www.ema.europa.eu/en/human regulatory/overview/medical-devices)

EMA – Expert Panel's activities on high-risk medical devices/IVDs

SME Info Day – 18 October 2024

Presented by Hilde Bastaerts, Scientific Officer, Expert Panels and Groups Office, Human Medicines Division, EMA

Expert Panel's activities on high-risk medical devices/IVDs

- Expert Panels composition and role, role of EMA
- Expert Panel's Activities in:
  - Scientific advice to manufacturers for high-risk medical devices
  - Support to manufacturers and notified bodies for orphan high-risk medical devices
  - Consultation procedures for certain high-risk medical devices (CECP) resp. high-risk in-vitro diagnostics (PECP)

Expert Panels – composition and structure of the panels

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Group of advisors set-up according to Articles 106 and 48(6) of the Medical Device Regulation (MDR) and the Regulation on *In Vitro* Medical Devices (IVDR), respectively, to support the **scientific assessment and advice** in the field of

`high risk`medical devices and **in vitro diagnostic medical devices**

Coordination committee

Chairs & Vice Chairs of 11 thematic panels + representatives of screening panel.

Expert panels

1. Screening panel (≈ 60 experts)

Thematic expert panels (≈ 80 experts + 20 IVD experts)

2. Orthopaedics, traumatology, rehabilitation, rheumatology (sub-groups)
3. Circulatory system (sub-groups)
4. Neurology (sub-groups)
5. Respiratory system, anaesthesiology, intensive care
6. Endocrinology and diabetes
7. General and plastic surgery and dentistry (sub-groups)
8. Obstetrics and gynaecology, incl. reproductive medicine
9. Gastroenterology and hepatology
10. Nephrology and urology
11. Ophthalmology
12. In vitro diagnostic devices

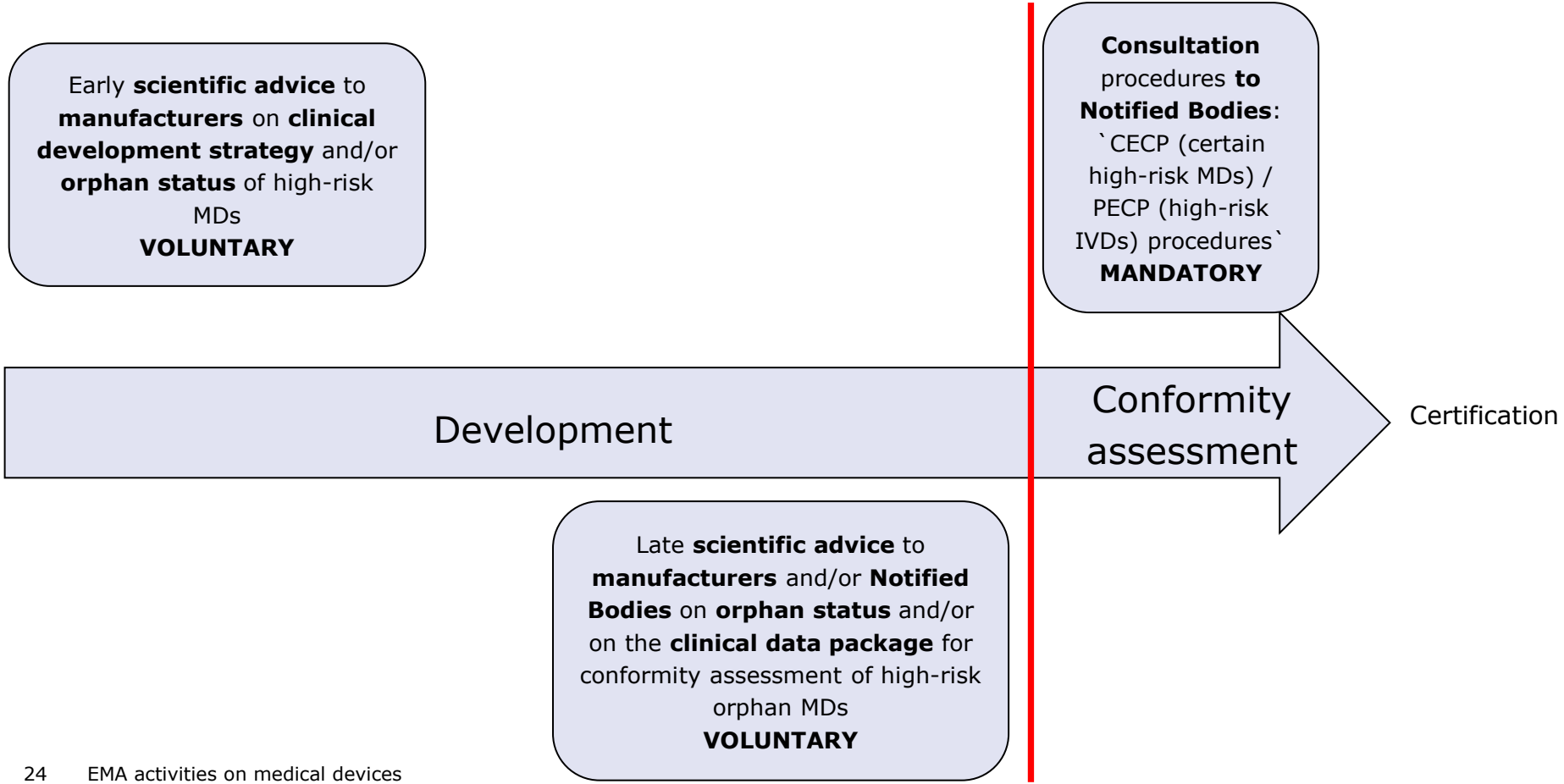
Central list of available experts
(≈ 125 experts)

Temporary assignment of experts to panels

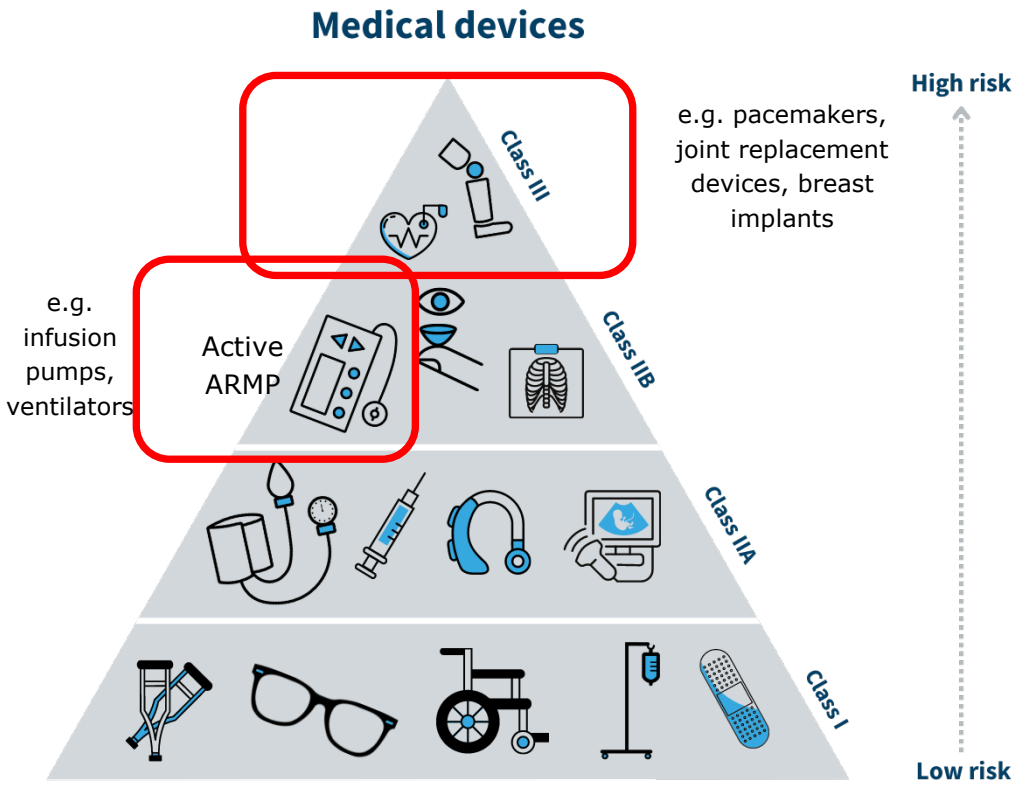
Reserve list for appointments

EMA provides administrative, technical and scientific support to the expert panels, in accordance with the Regulation on EMA's Reinforced Role (Regulation (EU) 2022/123).

Expert Panels – role of the panels



`High-risk` Medical devices



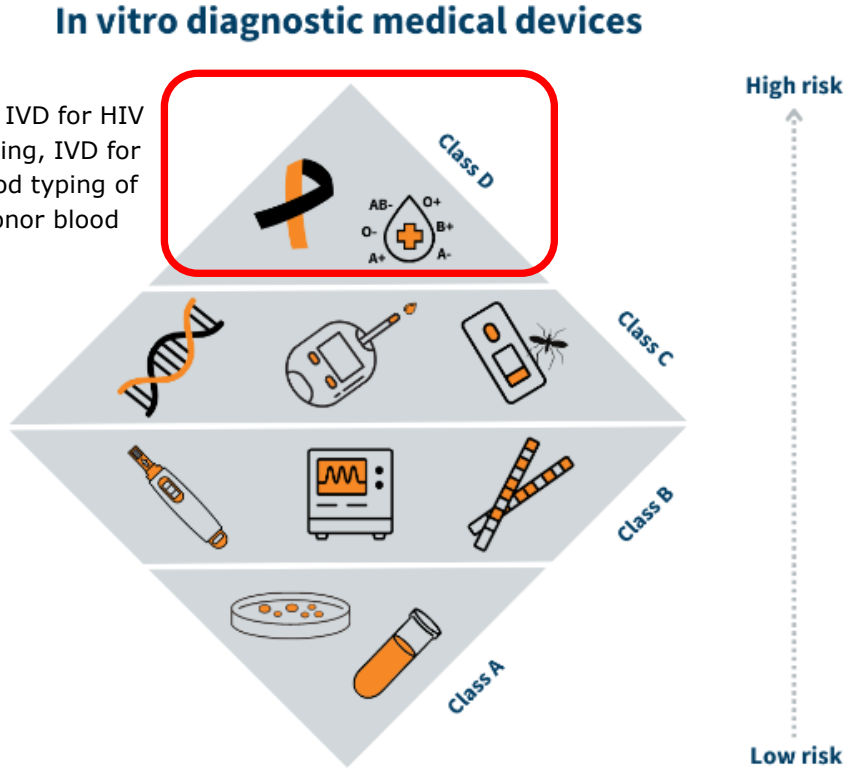
https://laegemiddelstyrelsen.dk/en/devices/

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for specific medical purposes (…)

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

Regulation (EU) 2017/745 – MDR

`High-risk` *In vitro* diagnostic medical devices



https://laegemiddelstyrelsen.dk/en/devices/

Any reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, (…), intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on physiological or pathological process or state, congenital (…), predisposition to (…) condition or a disease, etc.

Regulation (EU) 2017/746 – IVDR

Scientific advice to medical device manufacturers

EMA has been running a pilot that enabled the expert panels to provide clinical scientific advice for manufacturers of high-risk medical devices:

1st Phase:

- Started February 2023 - closed
- Purpose to pilot the service on a selection of products

2nd Phase:

- Started June 2023 - closed
- Purpose to pilot the service under conditions of higher demand

3rd Phase:

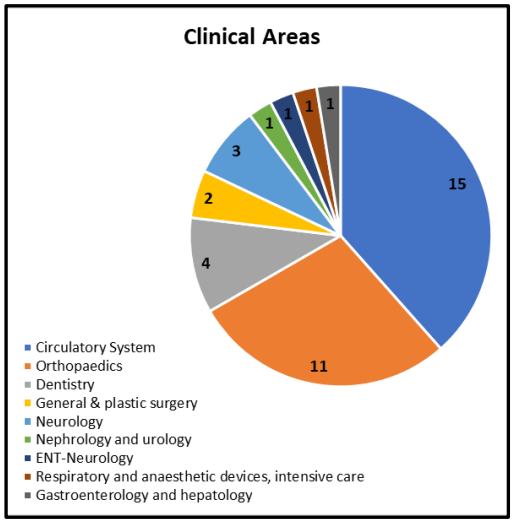
- Started April 2024 - closed
- Refine procedure and prepare for **regular service (expected in 2025)**

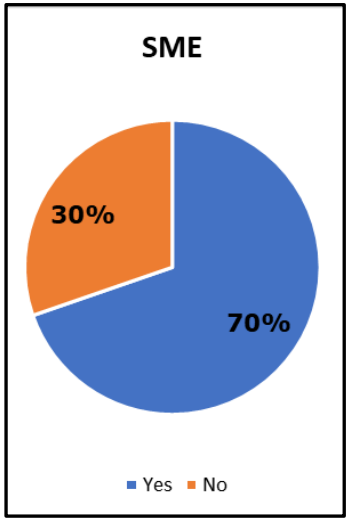
Questions from applicants are mostly on trial designs and clinical development strategy

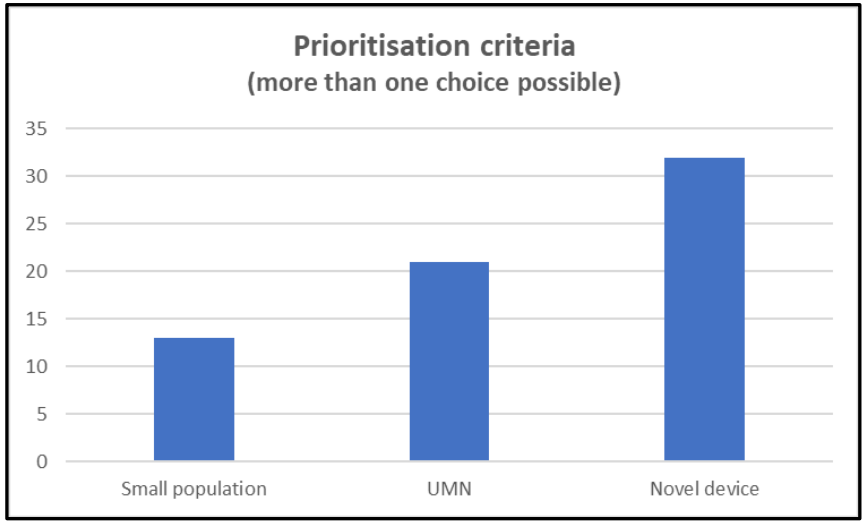
- Study Population
- Comparator
- Proposed endpoints
- Duration/follow-up
- Study design/type
- Biostatistics
- Post-market clinical follow-up (PMCF) plan

Pilot on Advice to Manufacturers

39 letters of interest for devices in the first two phases







Support for orphan medical devices

Orphan pilot – based on MDCG 2024-10 Clinical evaluation of orphan medical devices (europa.eu)

The ExP can assign an 'Orphan status' to a medical device if the following criteria are met:

- the device is specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year[1];
- and at least one of the following criteria are met:
  - there is insufficiency of available alternative options for the treatment, diagnosis, or prevention of this disease/condition, or
  - the device will offer an option that will provide an expected clinical benefit compared to available alternatives or state of the art for the treatment, diagnosis, or prevention of this disease/condition, taking into account both device and patient population-specific factors.

1. Extrapolated from population estimate criteria for HUD designation established by the U.S. FDA and calculated based on an EU population of 447 million

Support for orphan medical devices

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Orphan pilot – based on MDCG 2024-10 Clinical evaluation of orphan medical devices (europa.eu)

- **Started in July 2024 – runs until end of 2025, subject to available resources.**
- Focus on orphan medical devices and medical devices for orphan subpopulation – advice to manufacturers (early or late development) and/or to Notified Bodies* (late development) on:
  - a possible orphan device status
  - on the clinical evaluation of orphan medical devices

  * will submit their advice request in cooperation with the orphan device manufacturer
- Goal: help bring new orphan medical devices onto the EU market, while also keeping legacy orphan medical devices on the EU market

Support for orphan medical devices

The pilot programme will prioritise certain groups of orphan medical devices:

- Devices for treating medical conditions that are **life threatening** or cause **permanent impairment of a body function**
- Devices intended for **children**
- Novel devices with a potential **major clinical benefit**

For more information on the orphan pilot : see

Information session on the pilot for expert panels' advice for orphan medical devices | European Medicines Agency (EMA) (europa.eu)

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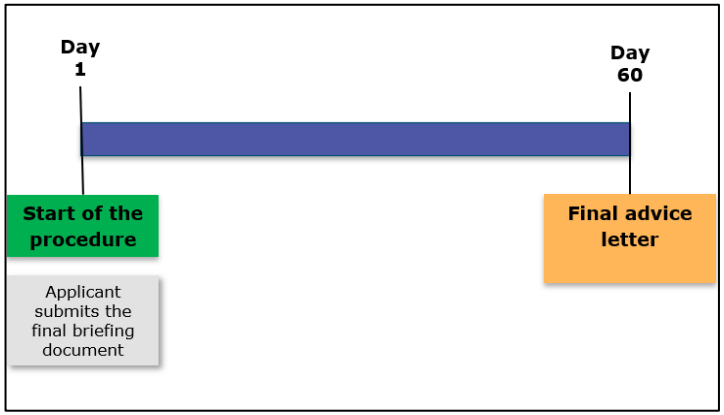
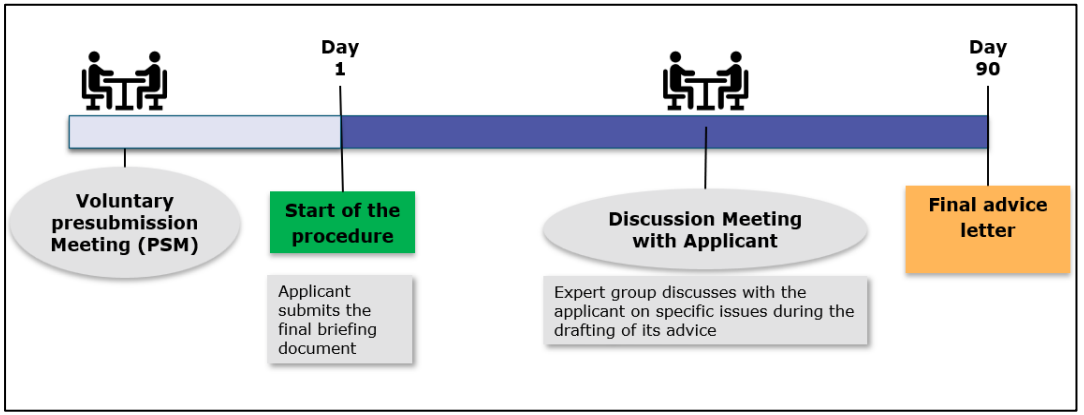
Scientific Advice Procedural timeline in the orphan pilot

OD status



OD status + clinical development



Consultation procedures (CECP/PECP)

For certain **high-risk devices**, the Regulations on Medical Devices (Regulation (EU) 2017/745) and on In Vitro Diagnostic Devices (Regulation (EU) 2017/746) require notified bodies to consult **expert panels** before issuing a CE certificate.

These high-risk medical devices include:

- Class III implantable devices and class IIb active ARMP devices
- Class D in vitro diagnostic medical devices

The **expert panels' opinions and views** are currently available on the European Commission's website:

- European Commission: List of opinions on class III implantable devices and class IIb devices under the CECP
- European Commission: List of views on class D devices under the PECP

Take home messages: activities of expert panels

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- Clinical advice to **manufacturers** of high-risk medical devices (pilots are closed, but in 2025 a **regular scientific advice** service will be implemented)
- In context of the ongoing '**orphan pilot**': advice to **manufacturers** of high-risk medical devices **and/or Notified Bodies** on:
  - the potential orphan status of a medical device,

  optionally in conjunction with
  - clinical advice (`early` or `late` advice' to manufacturers or 'late' advice to Notified Bodies)
- During conformity assessment of certain high-risk devices, **Notified Bodies must consult** the Expert Panels who provide:
  - an opinion on the notified bodies' assessment of the clinical evaluation (Clinical Evaluation Consultation Procedure (CECP) for medical devices)
  - a view on the manufacturers' assessment of the clinical performance (Performance Evaluation Consultation Procedure (PECP) for IVDs)

The EXPAMED Secretariat : EU-OPERATIONS-EXPAMED@ema.europa.eu

Abbreviations

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ARMP:	administer or remove medicinal product
CECP:	clinical evaluation consultation procedure
IVD:	in-vitro diagnostic medical device
IVDR:	in-vitro diagnostic regulation
MD:	medical device
MDR:	medical device regulation
OD:	orphan designation
PECP:	performance evaluation consultation procedure
PMCF:	post-market clinical follow-up

EMA’s activities to support development of medicinal products used in combination with medical devices or companion diagnostics

SME Info Day – 18 October 2024

Presented by Stiina Aarum, Senior Scientific Specialist, Scientific Advice, Product Development Scientific Support Department, Human Medicines Division, EMA

Presentation overview

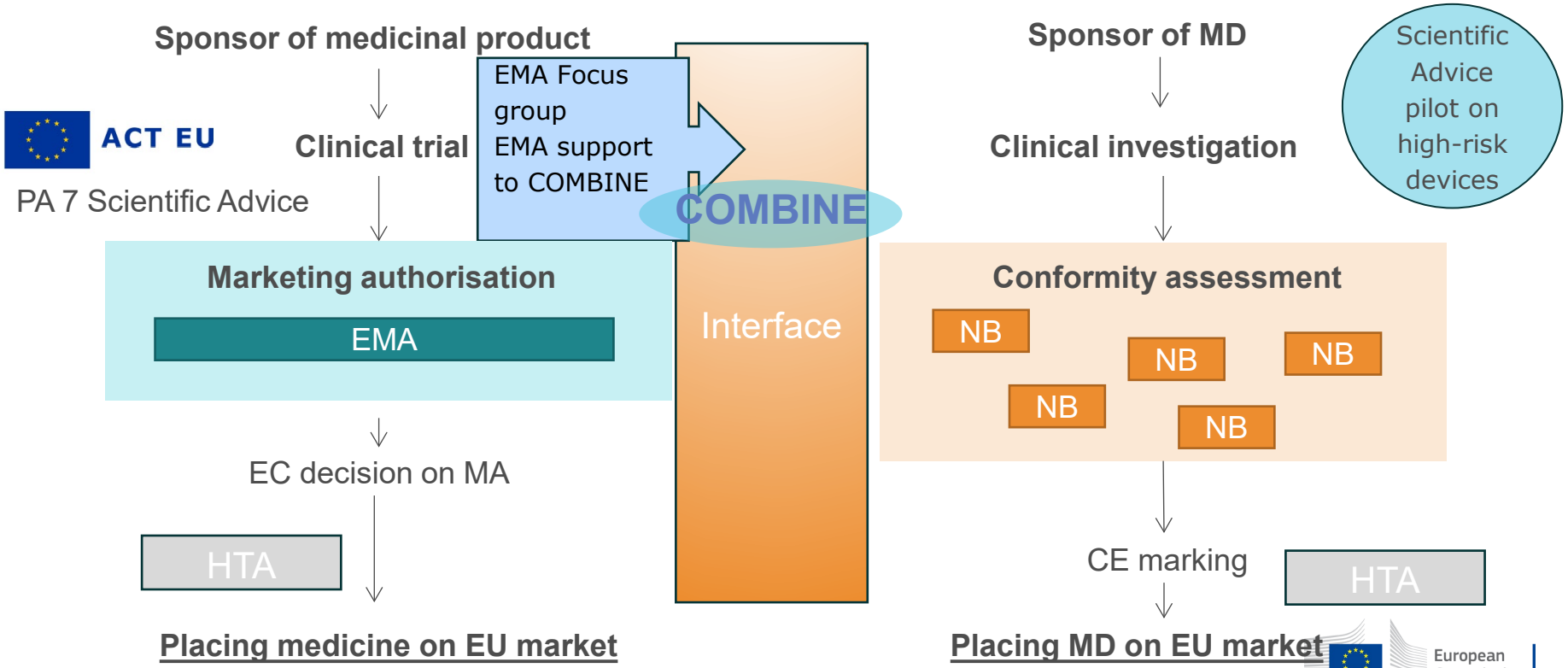
- Initiatives to support development and lifecycle management, with the focus on:
  - Focus group on the provision of Scientific Advice for medicinal products used in combination with medical devices or companion diagnostics
  - COMBINE
- EMA activities on Digital Health Technologies

Challenges on medicines used with medical devices or IVDs/CdXs in the EU

- The implementation of Regulation (EU) 2017/745 on Medical Devices (MDR) and Regulation (EU) 2017/746 on In Vitro Diagnostic Devices (IVDR) have changed the EU legal framework for medical devices, including new responsibilities for EMA, NCAs and NBs.
- Complex ecosystem for development and approval of combined products, with multiple actors and requirements. There is a need to develop more connectivity and synergies.
- Increasing numbers of combination products with higher complexity that require multidisciplinary discussions with multiple stakeholders.
- Combined studies pose a challenge, since they are regulated by 3 different frameworks (MDR, IVDR, CTR).

Combined study (informal definition): clinical trial of a medicinal product together with a performance study of an IVD or a clinical investigation of a medical device.

Initiatives to support development and lifecycle management



*edited

Focus Group on the Provision of Scientific Advice for medicinal products used in combination with Medical Devices or Companion Diagnostics (DDCs and DCDxCs)

- Developers raised the **need for scientific and regulatory advice** to ensure identification of appropriate development path of both medicine and medical device/CDx
- **Establishment of a Focus Group** (SAWP, NCA MD and IVD experts, industry, NBs, EMA) agreed at the EMA 9th R&D stakeholder platform meeting in Dec 2022, to explore options how scientific advice for DDCs and DCDxCs could be conducted to integrate different perspectives and to run a pilot.
- Analysis of 9 cases in 2023. Finally, not possible to initiate a pilot as NBs not allowed to engage in pre-certification discussions; rather to publish the results in a **Scientific publication** (final review ongoing) and other FU actions: exploring complementarity between SAWP and expert panel and the ev. involvement of NCAs with device competence in EMA scientific advice, continued collaboration with the EC, and to look into options and specific actions within ACT EU and COMBINE, review the (NBCG-Med) position paper.

Next steps for COMBINE

- **COMBINE** is a project launched by the Member States' competent authorities for clinical trials and medical devices and the EC aiming to analyse the root causes of the challenges encountered by sponsors in conducting combined studies and identify possible solutions to these challenges.
- First analysis phase with completed with report published:*Combined studies - European Commission (europa.eu)*
- Currently reshaping collaboration into step-wise **programme approach** for phase 2 to develop solutions
- Working across fields with established groups
- For sector-specific issues relevant to the interface, projects in each respective group
- Projects specific to the interface can be initiated and done jointly, overview of all ongoing work
- **EMA to continue supporting the programme**

1 – EMA activities on Digital Health Technologies (DHTs)

- Growing experience in **Scientific Advice and Qualification for DHTs used for evidence generation to support MP B/R assessment**; first DHT derived primary efficacy endpoint in clinical superiority trials of Duchenne's Muscular Dystrophy has been qualified (SV95c). Informal feedback also provided in ITF meetings. Cross disciplinary expert involvement
- **Published Questions and answers document (2020)**: Qualification of digital technology-based methodologies to support approval of medicinal products (link)
- We have also published an **article in NPJ Digital Medicine**, co-authored with industry on qualification of DHTs which includes regulatory considerations
- **Workshop on qualification of novel methodologies** (17-18 April 2023) had dedicated session on DHT/AI and ML based method qualification, WS report, Action plan
- **EMA internal Matrix activities**: Digital matrix, AI Coordination Group
- **Artificial Intelligence Reflection Paper** led by EMA Methodology Working Party (MWP) and recently published.

Take home messages

- EMA is fully committed to facilitate the regulatory interface between medical devices and medicines.
- Focus group explored multistakeholder scientific advice medicinal products used in combination with Medical Devices or Companion Diagnostics -publication underway.
- EMA to continue its support to the COMBINE programme.
- Formal and informal forums for discussion with multidisciplinary groups are in place to foster increased dialogue and engagement.

Thank you for your attention

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