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Combined developments
CTR, MDR, IVDR

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Disclaimer

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- **EMA**: “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.”

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Legal placement

Do I need to consider additional legislations?

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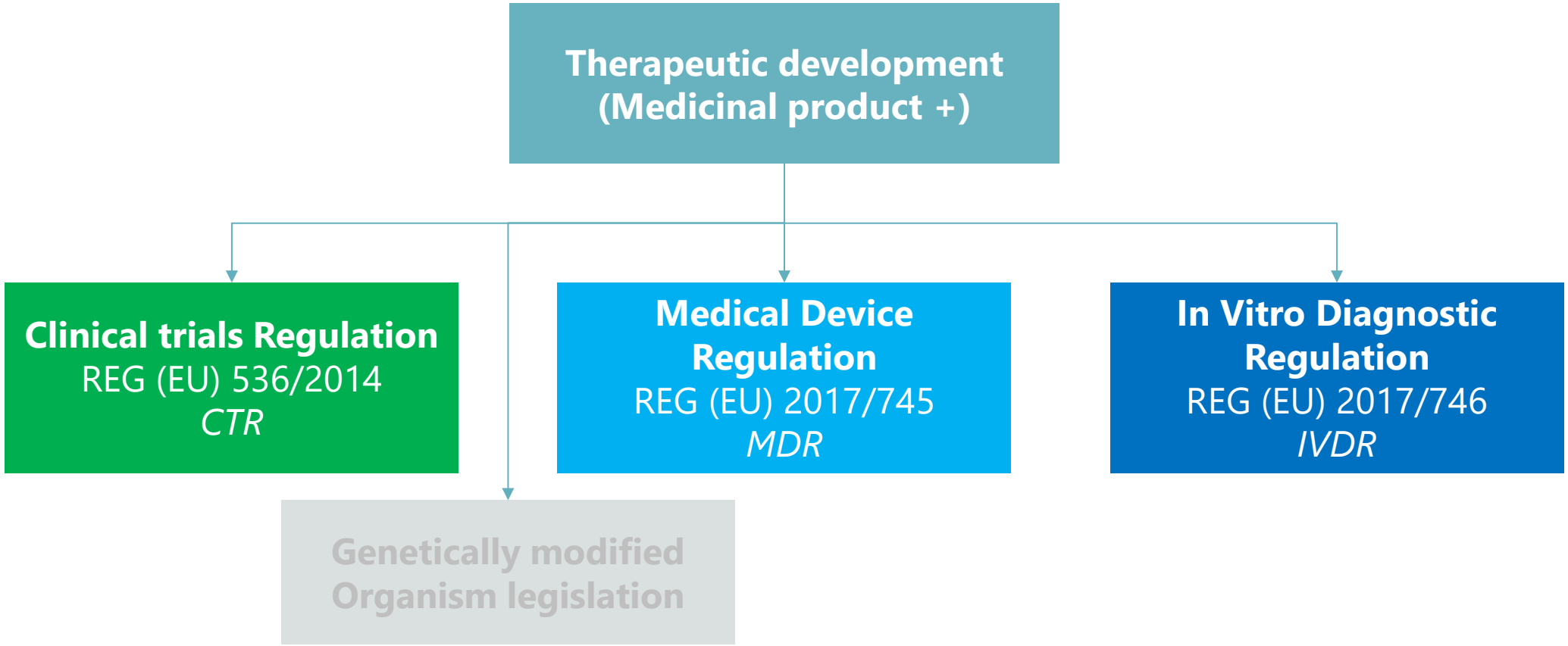

Legal placement – Why is this relevant?

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The European Legislation currently does **not** allow a single approval process for the simultaneous investigation of medicine and medical device/IVD

Goal of the investigation	**EU Framework**
Investigational medicinal product	Clinical trial (CTR)
..if GMO, additional approvals needed	Dir/2001/18/EC, Dir/2009/41/EC
Investigational/non CE marked medical device	
Integral device - Art. 1(9) MDR	Clinical trial (CTR)
Non-integral device (co-packaged)	Clinical investigation (MDR)
„Referenced" administration device	Clinical investigation (MDR)
Investigational/non CE marked IVD	Performance study (IVDR)

Information to be provided in a CT application

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Cover letter

- CTR Annex I.B.7 (i): sponsor to include in the Cover letter the list of medical devices/IVDs to be investigated in the CT, which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended purpose.

  → to be understood to refer to medical devices/IVDs which are specifically required by the protocol to be used to achieve the objectives of the trial, e.g. not all

- If not CE marked **for the intended purpose** → investigational
- Need for parallel clinical investigation/performance study – process depending on nature of the device/IVD

ATMP-device

The scenarios for medical devices

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A device is only legally on the market, if certified **for the intended purpose**

- ATMPs with **non-integral** co-packaged or referenced medical devices:
  Device is independent entity subject to the MDR. In the clinical trial, the potential impact of the device on the quality, safety and/or efficacy of the ATMP needs to be addressed and the safe and effective use of the medical device in combination with the ATMP be supported by data

  example: refillable administration devices, dedicated surgical tools

- ATMPs with an **integral** medical device:
  Overall product is governed by medicinal product legislation "only". Scientific data have to be proportionate to the role in the product. Data supporting the safe and effective use need to be submitted with specific reference to relevant General Safety and Performance Requirements (GSPR) of the MDR.

  example: device is part of the product administered

Summary - simplified

Assumption medical device without CE mark for intended purpose

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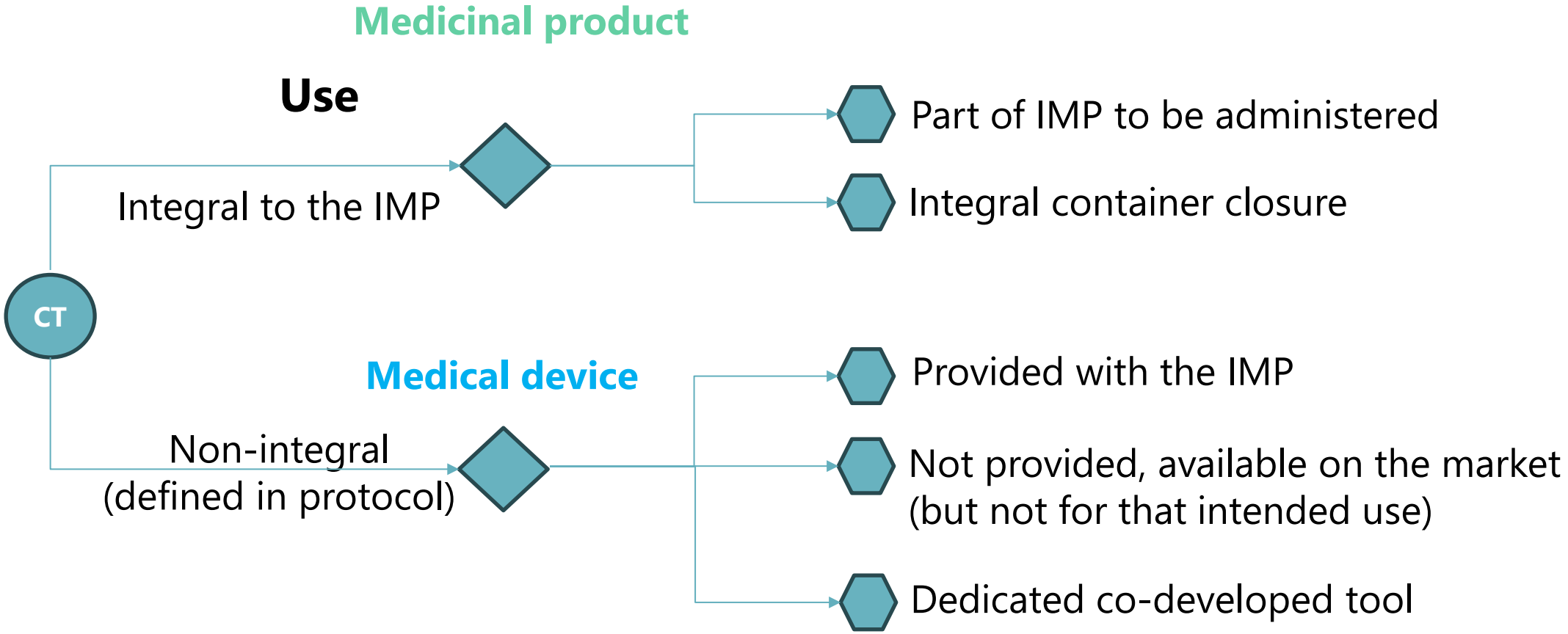

When is a test/assay an IVD from a clinical trial perspective?

..or a CDx under development

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Biomarker ⟷ **Biomarker-Assay**

Needs to be justified for the clinical trial

IVD/CDx — Not *a priori* an IVD

Therapy deciding/ interventional

- *Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)*
- *Q&A on Complex clinical trials (Q5)*

See EudraLex Volume 10, Chapter V https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en

Depends on use within the clinical trial (protocol)
and
Whether or not development as IVD/CDx is intended
Either way, suitability for the CT is required

What is a companion diagnostic (CDx)?

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Concept introduced through the IVDR

- „Companion diagnostic' means a device which is essential for the safe and effective use of a corresponding medicinal product to:

  - identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
  - 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;

- Devices that are used with a view to monitoring treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be CDxs.

IVD - Performance Studies

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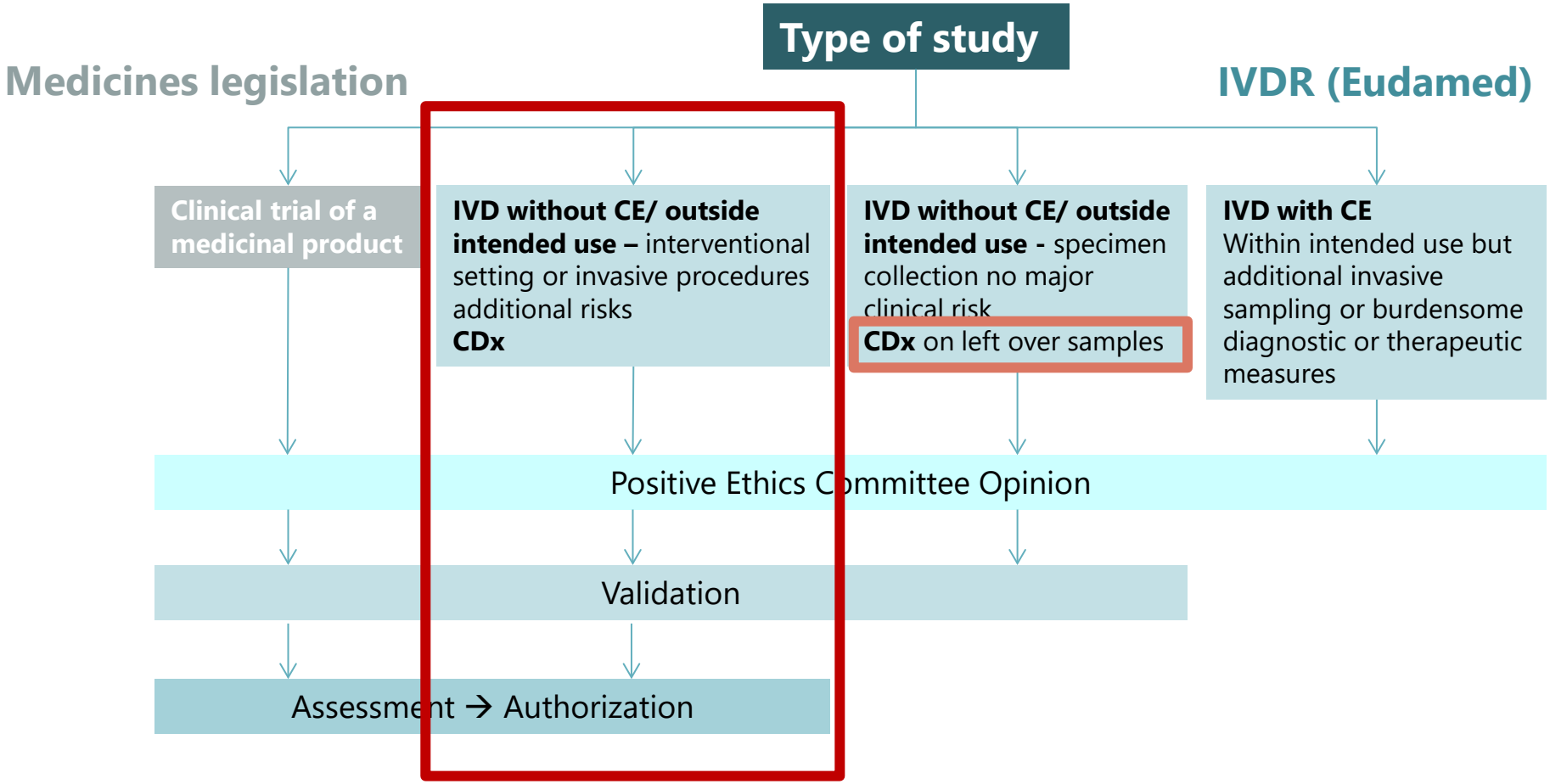
Submission/approval process



In-house assays…

Article 5 4) and 5) IVDR and the need for performance studies

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- IVDR Requirements do not apply to devices manufactured and used only within health institutions established in the Union, provided that they comply with the applicable provisions laid out in that Article 5 (5), which includes compliance with relevant general safety and performance requirements (GSPRs) set out in IVDR Anx I
  → no general need for performance studies

However:

- If a study is intended to establish/confirm the performance of a new/or existing device outside its intended purpose → device cannot be considered to fulfil the relevant GSPRs, in particular those related to clinical and/or analytical performance.
  → study is a performance study, Article 57 and Article 58 apply

In-house assays

Article 5 4) and 5) IVDR *(shortened)*

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- In-house assays do not need performance studies *a priori*, but it is a performance study, if they are being investigated
- Using an in-house IVD as interventional assay is possible in clinical trials but generates complexities later →
- Use outside the health institution not feasible
- Not suited for medicines at marketing authorization (different locations)
- Use no longer permissive is CE marked IVD/CDx becomes available

- Theoretical option of using different in-house assays at treatment sites → How to guarantee equal assay performance?

Summary - simplified

Assumption assay without CE mark for intended purpose

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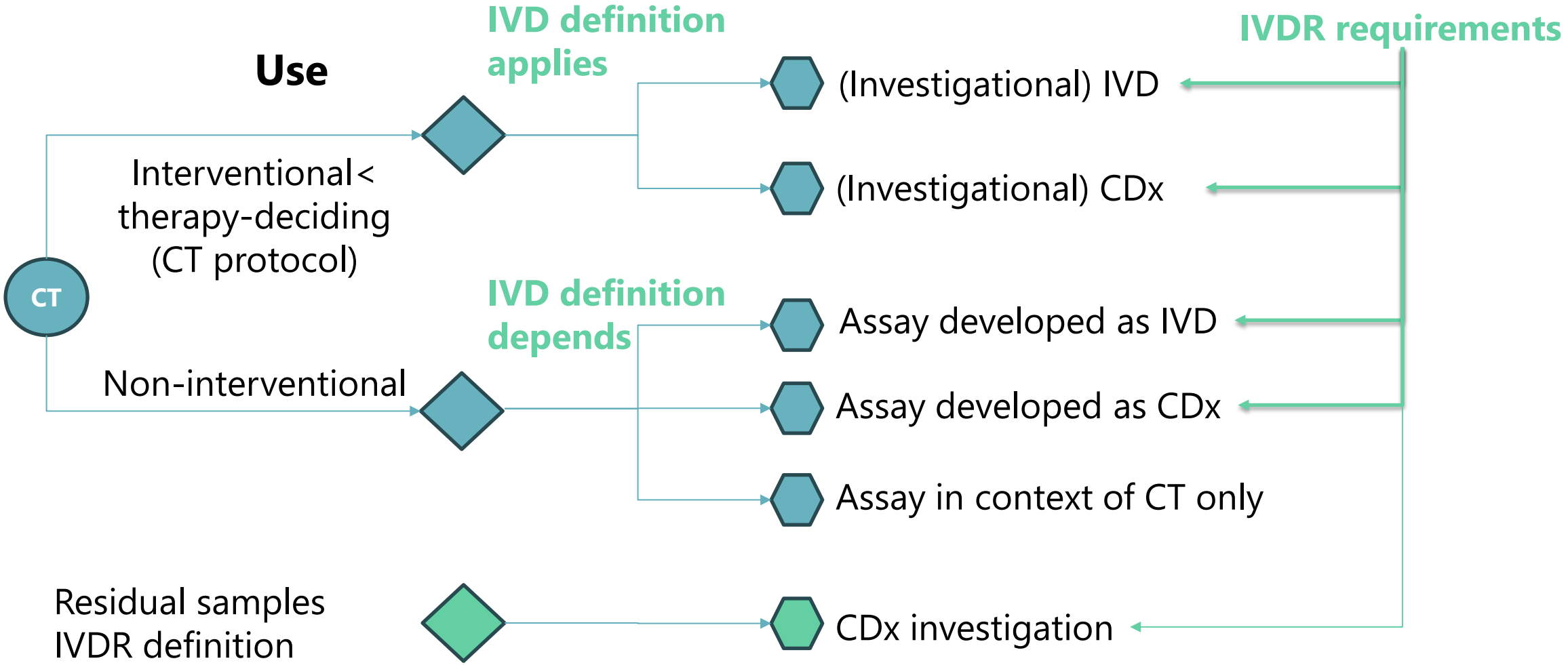

Regulatory activities

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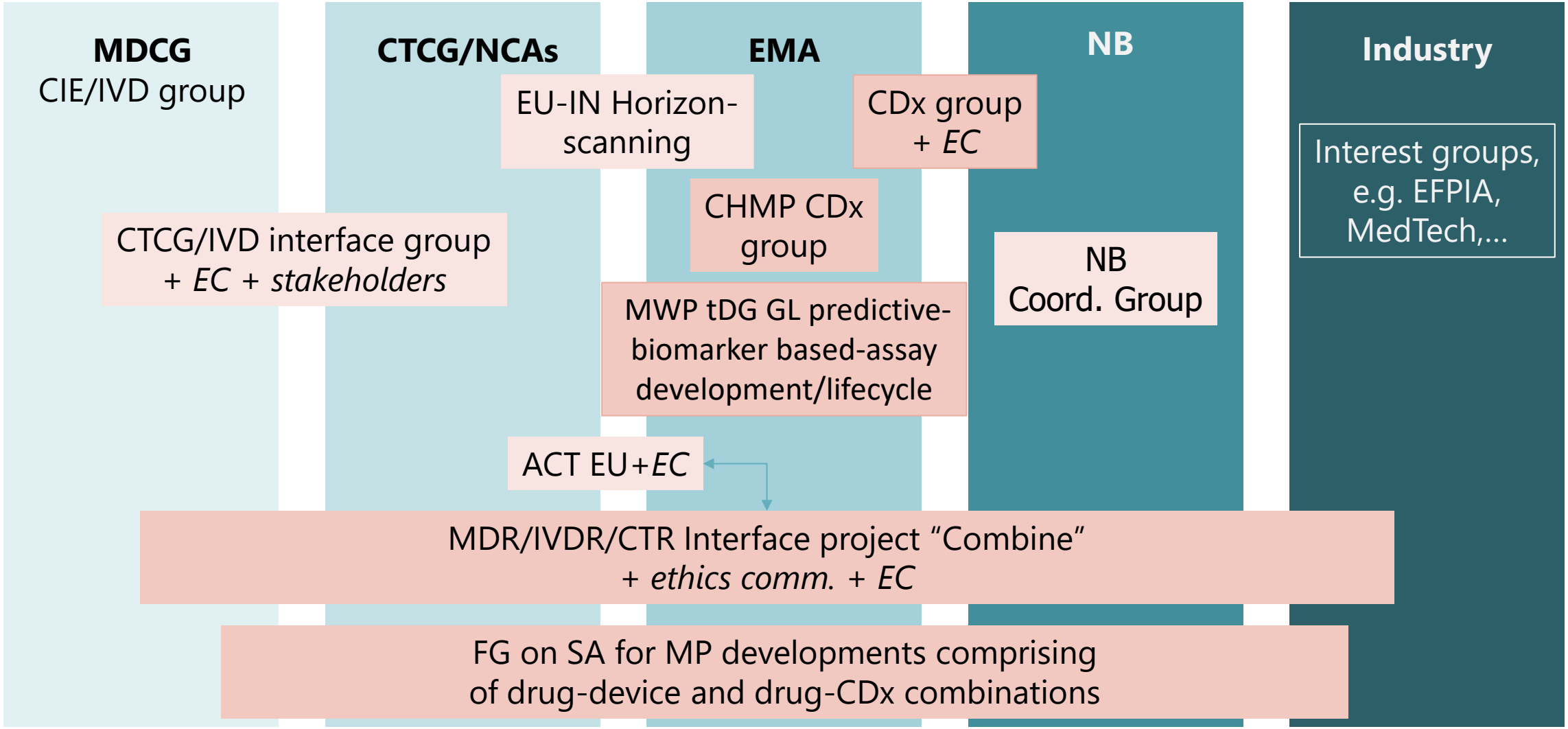

Thank you for your attention!

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In-house assays

Article 5 4) and 5) IVDR *(shortened)*

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- Devices that are manufactured and used within health institutions,
- Relevant general safety and performance requirements (GSPRs) in Annex I apply
- Conditions to be met:
  a) devices are not transferred to another legal entity;
  b) manufacture and use occur under appropriate quality management systems;
  c) the laboratory complies with EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;
  d) the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market;
  e) the health institution provides information upon request on the use to its competent authority, which shall include a justification of their manufacturing, modification and use;

In-house assays

Article 5 4) and 5) IVDR *(shortened)*

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a) the health institution draws up a declaration which it shall make publicly available, including:
   i. the name and address of the manufacturing health institution,
   ii. the details necessary to identify the devices,
   iii. a declaration that the devices meet the GSPRs set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification;

- Using an in-house assay in a core-facility concept for a multicenter/national clinical trial is acceptable. Samples may travel.
- Information to be provided in a CT: the name of the health institution where the IVD is manufactured and used and a link to their IVDR Art 5(f) declaration.
- **No** need for parallel performance study reporting

USA

Framework for Laboratory-developed Tests (LDTs)

- April 29, 2024: FDA announced a final rule aimed at helping to ensure the safety and effectiveness of laboratory developed tests (LDTs). The rule amends the FDA's regulations to make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. FDA is finalizing a policy under which FDA will provide greater oversight of IVDs offered as LDTs through a phaseout of its general enforcement discretion approach for LDTs over the course of 4 years, as well as targeted enforcement discretion policies for certain categories of IVDs manufactured by laboratories
- May 14, 2024 FDA webinar to provide an overview of the final rule, including the phaseout policy.
- https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests