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Interfaces -
Clinical trials, assays and In-vitro-diagnostics

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- I attend this conference as an individual expert.

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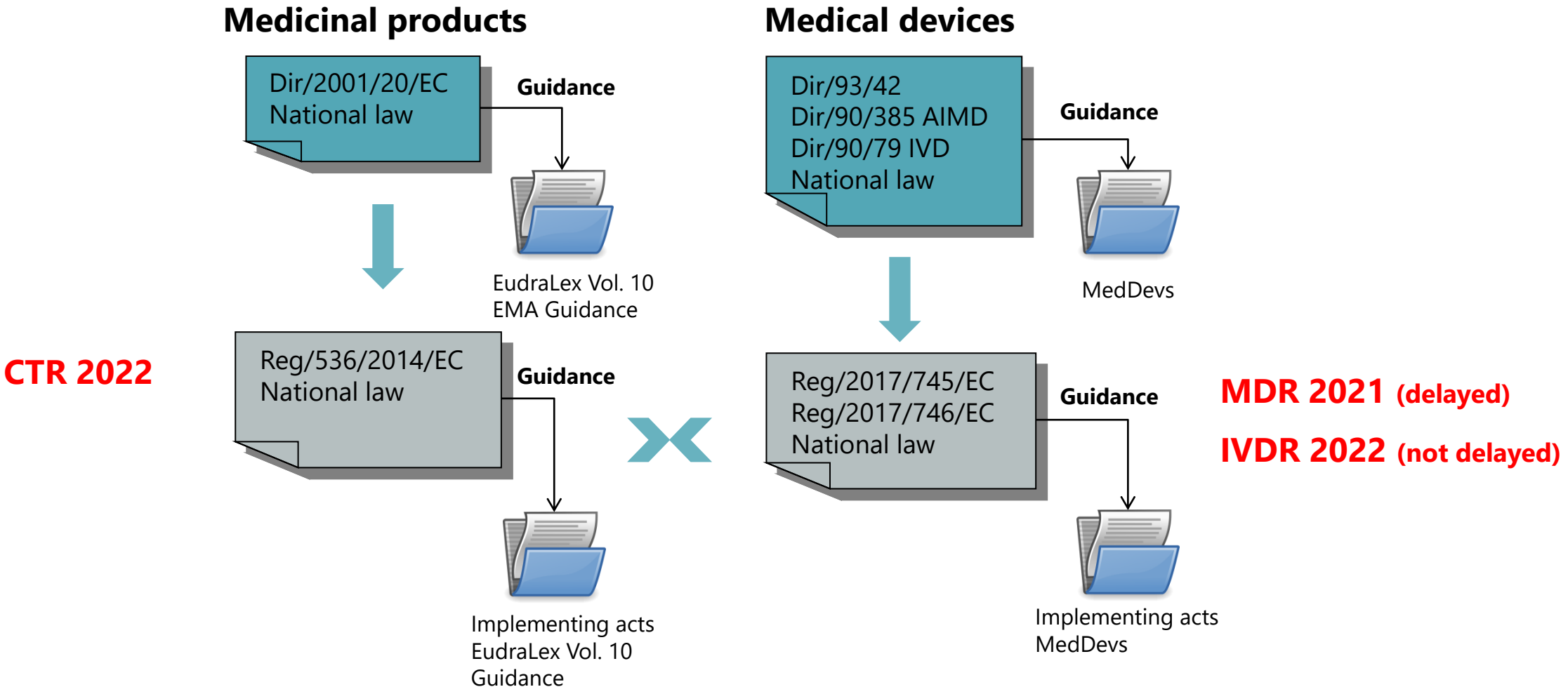
Introduction

Legal Starting point



Introduction

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Why do we need to discuss this now?

- The IVD definition is changed compared to current legislation
- The companion diagnostic concept is introduced
- IVDR leads to reclassification of IVDs → a higher percentage of IVDs will require Notified Body approval (10% → 80%)
- Medicinal product and IVDs development may coincide
- Developers need clarity on requirements at the intersection of legislations
- The transition between scientific assay - IVD and companion diagnostic is fluid. It is to be expected, that during pivotal trials even assays intended for commercialization will not (yet) be CE marked (due to the need to generate clinical evidence)
- Need to have a big picture view on legal text, process manageabilty and scientific requirements → to ensure patient safety, robustness of data, planning security for developers

CTR - IVDR

Why is the discussion complex?

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- Legislations are introduced for a reason – reproducibility/oversight
- Solely need for interoperability of databases in legislation (interface) → drafted „in isolation“
- Legal feedback: Clinical trials are not a “safe haven” for IVDs → IVDR requirements do apply
- Where the system implementing new legislations, interfaces are not prioritised
- Introduction to the market (which includes CT sponsors) of IVDs is covered by the IVDR
- The intent to develop an assay as IVD is not verifyable by the agency/not necessarily known by the developer at the time of CT submission
- Product-/program-specific assays in a CT are not necessarily, but possibly, intended to be developed as IVDs (e.g. immunogenicity assays, assays for new biomarkers)
- Legal feedback – CTs are only legally compliant if ALL tools used are compliant

  → responsibilities regulators?

Interfaces in Clinical trials

What are the issues

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- Legal wording does not take interfaces into consideration
  - Same principles as basis for legislation, e.g. subject safety, robustness of data
  - But separate legislations
  - Real life does not allow for the desired black and white separation of responsibilities
- Historically - Procedures are not aligned
  - From the developer‘s view it is „one development“ that needs to be split in two processes
  - The MDR/IVDR improve timelines, but the processes are independent
- Documentation/Scientific assessment
  - From the developer‘s view - „one development“
  - From the assessor‘s view it is „one development“, but includes aspects where multiple expertises are needed
  - A relevant assessment requires more than just the documentation on one part, e.g. the medicines → while separtion of responsibilies might be achievable, separation of information does not make sense.

MDR

Definition Medical Device Art. 2 (1)

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'**medical device**' means 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 one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

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.

Evolving definitions

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Directive 98/79/EC (IVDD)

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, 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 (one):

- concerning a physiological or pathological state
- concerning a congenital abnormality
- to determine the safety and compatibility with potential recipients
- to monitor therapeutic measures

Regulation 2017/746 (IVDR)

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent apparatus, piece of equipment, software or system, whether used alone or in combination, 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 one or more of the following:

- concerning a physiological or pathological process or state;
- concerning congenital physical or mental impairments;
- concerning the predisposition to a medical condition or a disease;
- to determine the safety and compatibility with potential recipients;
- to predict treatment response or reactions;
- to define or monitoring therapeutic measures

Where will we see co-developed IVDs?

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Personalized therapy

Personalized/ individualized manufacture

Medicines produced with a consistent manufacturing process but autologous starting material, e.g. CAR T cells

Medicines produced with a consistent manufacturing process but patient-specific targets, e.g. RNA based approaches

Medicine produced with a manufacturing process and target unique to a patient → individual preparation

Molecular versus clinical symptomatic indication for a drug

„Molecular" indication coupled to biomarker detection → companion diagnostics

Patient specific therapy based on molecular profiling

Personalized therapy

Complexity

personalized

No new „product" but therapeutic optimisation with existing medicinal products and medical devices/IVDs

individualized

What is a companion diagnostic (CDx)?

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Concept introduced through the IVDR

- „Companion diagnostic' means a device which is <u>essential</u> 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 companion diagnostics

Who decides?

- IVD manufacturer submits certification application for CDx to Notified Body

„Legacy CDx“

.. And requirements

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- There is no transition period for IVDs that require it under the IVDR but did not require NB certification under the Directive → which applies to all CDx
- → need to be Certified for the intended purpose by the date of IVDR
- → need to have undergone the consultation process by then
- „New“ CDx will be subject to IVDR requirements

- CDx Group at EMA – close interaction with NBs on content and procedure

Regulatory Stakeholders for products with device/IVD aspects

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… or „why is it complicated?“

Development (trials)

NCA - medicines | NCA - devices *

Ethics committee

Clinical study lifecycle, inspections

Authorization/ Certification

EMA | NCA - medicines | Notified Body

** One or more entities*

License / Certification

Post-Authorization/ Certification

EMA | NCA - medicines | NCA - devices * | Notified Body

Vigilance / post-marketing oversight, inspections

Assays in clinical trials

- Most assays in CTs fulfill IVD definition and are applied within certified intended use or according to in-house exemption
- Some assays are performed for exploratory purposes and not necessarily meant for development towards certification

Serum Chemistries	Hematology[a]	Urinalysis With Microscopic Examination	Screening Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Direct/indirect bilirubin (if total bilirubin is elevated above ULN) Ferritin (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements) Folic acid (screening visit) Glucose Iron (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements) LDH Phosphate Potassium Sodium Total bilirubin Total protein Total iron-binding capacity (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements) Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count RBC count WBC count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody Hepatitis C virus antibody Hepatitis C virus-RNA (only performed if antibody positive) HIV antibody Anti-streptolysin antibody Anti-phospholipid antibody	D-Dimer
		Hemolysis Markers		
		Haptoglobin LDH (will be measured in serum chemistry panel) Reticulocyte count (will be measured in hematology panel) Hemoglobin (will be measured in hematology panel) Total bilirubin and direct/indirect bilirubin (will be measured in serum chemistry panel)		
		DAT and Cold Agglutinin Test		
		DAT for IgG and C3b* Cold agglutinin levels* * Baseline and EOT		
		Other Assessments		
		Urinalysis FSH Urine pregnancy test (at site) Serum pregnancy test Complement assessment (CH50, C3, and C4)* * Baseline and EOT Vitamin B12 (screening visit)		

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.
[a] Hematology parameter may be managed in a real-time in a local laboratory.

The „product“ concept

.. And similarities to assays used in CMC development

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- A medicinal product is an entity

- An IVD can be „placed on the market or put into service“
  - A product, e.g. a device for self-testing
  - A (commercial) service
  - An in-house IVD (health institution) Art. 5 (5) IVDR

- Why do I stress this? – It is in the „non-products“, where we have the closest overlap with assays performed in the context of CMC development, e.g. the analytes are different, the technology similar, validation requirements apply

Interface group

CTFG – MDCG IVD

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- The Clinical Trials Facilitation and Coordination Group (CTFG) and the MDCG IVD Group set-up a joined taskforce to address interface issues.
- The project governance structure include CTFG (a Heads of Medicines Agencies working group), the relevant IVD and CT parties in the EU commission and other stakeholders such as EMA
- Question & Answer document to clarify requirements
- Was supposed to be finalized in July – end of year more realistic

Status quo

CTR - IVDR

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- 2 years of discussions, Q&A to be finalized soon
- Living document, further Q&As can be added
- Uncertainty on the side of assessors of CTs on what we will have to verify compliance with, e.g. CTR and IVDR? → responsibility and training
- More attention to assays/IVDs needed ← information to be provided to assess the robustness of data to be generated in the trial
- More awareness of requirements by the assessor is not appreciated by applicants, because „in other member states we got the trial approved without the need for a performance evaluation/extra requirements“

Which assays are to be considered IVDs? Proposal

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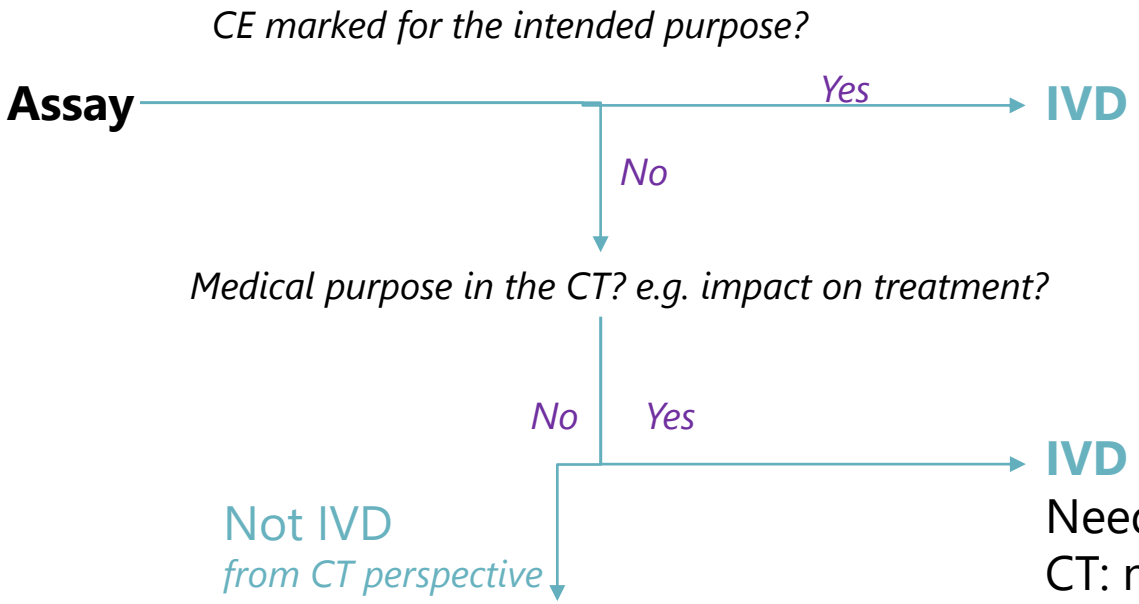
Interface group CTFG MDCG-IVD



The Sponsor is responsible for CT participant safety and robustness of data and needs to be compliant with ICH GCP E6 (R2)
→ includes suitability of "tools" used
Documentation in TMF/site file

IVD
Need for parallel performance study
CT: need for data to demonstrate suitability for the intended purpose

Supportive data, where requested.
Sponsor/developer's responsibility to comply with IVDR requirements, where data are generated for the performance evaluation of an IVD

Art. 2 (1) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease

IVD - performance studies

Approval process

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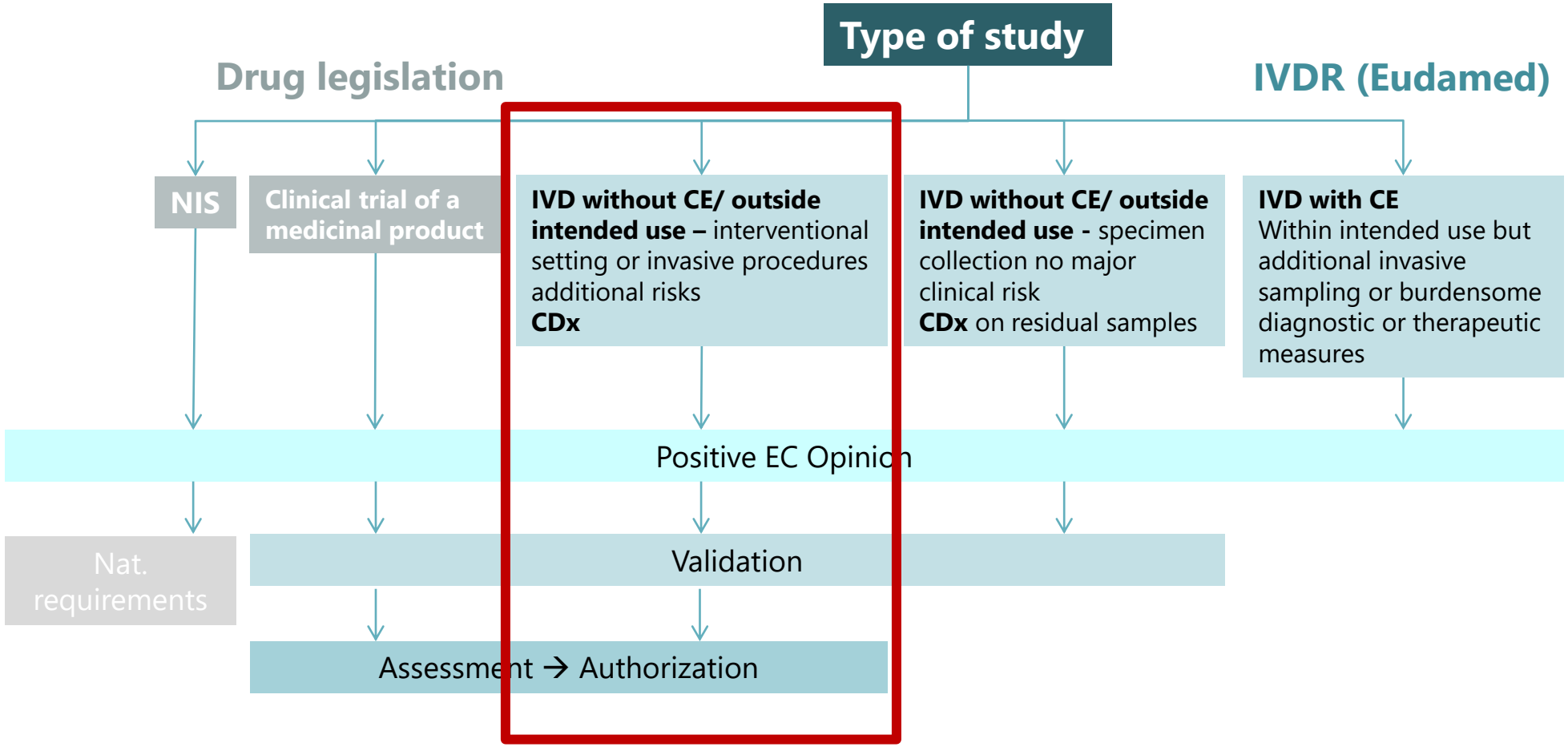

My personal opinion

Scientific perspective

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- IVDs are „products“ or assays made from scratch
- The medicines framework has the competence to evaluate assays in the course of medicines development (CTA, MAA), if provided with the information
- There is no need for additional competence for assays (in contrast to IVD products: device design, manufacturing aspects etc.)

BUT:

- The information needs to be provided and part of the dossier
- The assessment needs to be collaborative (Q, NC, C as needed)
- Potentially more focus needs to be placed on assay assessment

Of note, immunogenicity assays are found in the quality part of an IND in the US, but not in the EU.

Information content for non CE marked IVDs

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That have an impact on patient treatment in CTs

- Background
- IVD description
  - System description
  - Assay technology
- Use of the investigational IVD in the CT
  - Intended use
  - Population
  - Sample type
- Study risk determination
  - Risk of false results
  - Risk of a false positive result
  - Risk of a false negative result
  - Risk of a delayed result
  - Conclusion
- Status of analytical qualification/validation

Device design

Quality

Preclinical
Clinial

One project – two trials

CT submission

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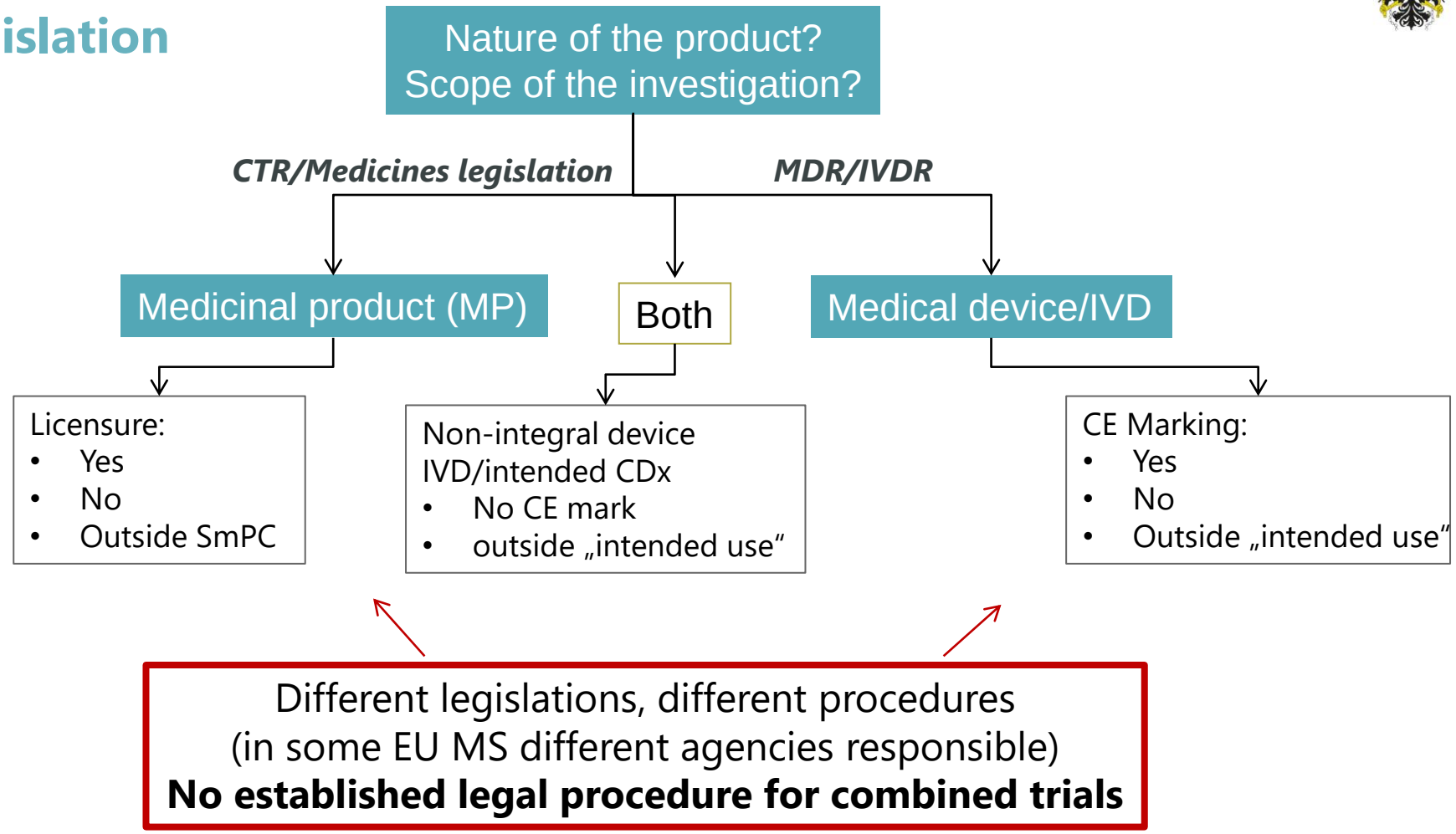
- What the European legal system currently does **not** provide for is a single process for approval of a trial according to both legislations
- Parallel submission might be easier in member states, where the same agency is responsible for both legislations, or where cooperation between agencies is well established
- Different document-requirements
- Balance between separate requirements and the need for information to understand the entire project

- Austrian experience – same division responsible for trials according to both legislations
  - Challenge to integrate documents
  - Need for collaborative assessment medicines/medical devices
  - Need for collaborative assessment Q/NC/C, particularly for complex products

Clinical studies

Applicable legislation



IVDR Article 69 2) When setting up the electronic system .., the Commission shall ensure that it is interoperable with the EU database for CTs … as concerns combined clinical investigations of devices with a CT under that Regulation.

Interplay with the MDR

Issues are similar

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- The situation with the MDR is somewhat easier because
  - We are dealing with products
  - Non-integral devices can be assessed separately
- However, we have the same questions on parallel CT submission processes and alignment of opinions

- Integral devices
  - Article 1(9) MDR → integral devices for delivery of medicines fall under medicines framework
  - Article 117 does not apply during CTs
- Non-integral devices
  - Need for reporting according to MDR
  - → procedural and assessment questions

Conclusion

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- A dedicated EU (legal) strategy is required, specifically for interface issues, to
  - Clarify priorities
  - Help to solve potential conflicts/lack of interface between legislations
  - Provide for science based pragmatic solutions
  - Deal with innovative products that would fall under multiple legislations

- **We have work to do!**

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Thank you for your attention
Questions?