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The Regulatory Interface of ATMPs and Medical Devices in Europe

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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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ATMPs and medical devices in the EU

Legislation and interfaces

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ATMPs

Dir/2001/83/EC … Medicines

Reg/726/2004/EC … EMA/centr. MAA

Reg/1394/2007/EC … ATMP

Reg/2014/536/EC … ClinTrial

Co-development

Legal, Procedural and Scientific Interfaces

Medical devices

Reg/2017/745/EC … devices
Incorporates Clinical investigation requirements

Reg/2017/746/EC … IVDs
Incorporates performance study requirements

ATMPs and medical devices

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Not all ATMP device combinations are “combined ATMPs“

Combined ATMP according to ATMP Regulation definition

- ATMP has one or more **integral** medical devices (MDs) or active implantable MDs components in scope the EU medical device legislation (integral - single integral product, intended exclusively for use in the given combination, not reusable)

  example: viral vector in prefilled syringe

ATMP with non-integral devices (co-packaged, referenced) ≠ combined ATMP

- A medicinal product with non-integral medical device(s) necessary for administration, correct dosing or use

  example: cartridge co-packed with an automated mini-doser

ATMP to be used with a referenced (not co-packaged) medical device (← SmPC)

example: ATMP to be used with a dedicated surgical tool, e.g. syringe applying precise low volumes

What is an integral device?

In the context of EU medicinal products/ATMPs

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- What matters is the presentation of the product at the moment of the placing on the market, not at the time of administration → 3 cumulative conditions

1. the device and the medicinal product form a single integral product
2. intended exclusively for use in the given combination
3. which is not reusable

- **ATMPs:** Annex I to Directive 2001/83/EC clarifies that combination of the medical device with the cells at the time of administration can be considered as an integral part of the finished product.

Medical devices for manufacture

Relevance of the CE mark

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- Medical devices for manufacture are not integral medical devices
- If equipment used to isolate/manipulate cells/tissues is CE marked as medical device, this applies only to a specific intended use, e.g. „separation of cells“
- The CE mark cannot apply to the resulting product, which is a cell based medicinal product ← immanent pharmacologic, immunologic, metabolic action
- → The user of the device becomes the manufacturer of a medicinal product → lack of awareness with users
- Technologic advances permit substantial manipulation → gene therapy in a private practice setting is technologically feasible

Legal responsibilities for authorities in the EU

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ATMPs and devices

** One or more entities*

Development (trials)

NCA - medicines | NCA - devices * | Ethics committee

Clinical study lifecycle, inspections

Authorization/ Certification

EMA — *License*

Notified Body — *Certification*

Post-Authorization/ Certification

EMA

Notified Body

Vigilance / post-marketing oversight, inspections

Which Notified Body?

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Whose responsibility?

- The responsible National Competent Authority for Clinical trials is determined by the location (e.g. responsible member state)
- ATMPs undergo mandatory centralized marketing Authorization → EMA/CAT
- The choice of Notified Body is up to the developer and not determined by location

An MAA applicant for a combined ATMP …

- is requested to identify a NB in the Application form even in the case where NB assessment of the device component has not yet taken place
- should ensure this NB is notified for assessment of the type of device in the combined ATMP ← consider the experience of that NB with similar products

Procedural aspects during development

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The European Legislation currently does not facilitate the simultaneous investigation of medicine and medical device/IVD in a single process

Goal of the investigation	**EU Framework**
Investigational medicinal product	Clinical trial (CTR)
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)

→ One project could have multiple reporting requirements, potentially to different agencies and member states

Procedural aspects at Marketing Authorization

ATMPs versus other medicinal products

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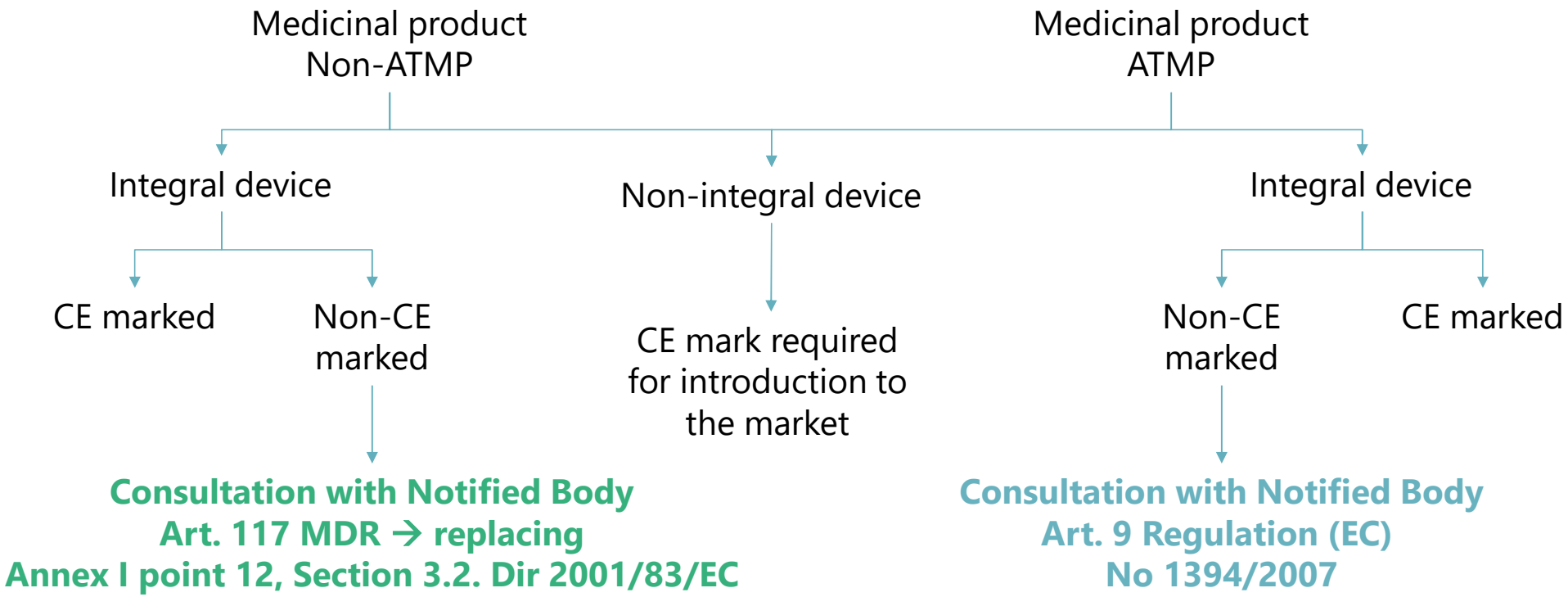

* CE-marked = CE marked for the intended use
Note, the slide is simplified and does not consider legal exceptions

Article 9 REG (EC) No 1394/2007

Consultation of a Notified Body - When and how?

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- CAT to decide that NB consultation is needed
- NB assessment on the device part, if presented at MAA to be recognized
- When required it likely in the form of a list of questions

- When is it potentially needed?
  - When existing NB opinion relates to a different intended use
  - When the combination with the ATMP may have an effect on the original technical, clinical and biological characteristics of the device →
    focus on safety and performance of the device part

The consultation process

Communication according to art. 9 REG (EC) No 1394/2007

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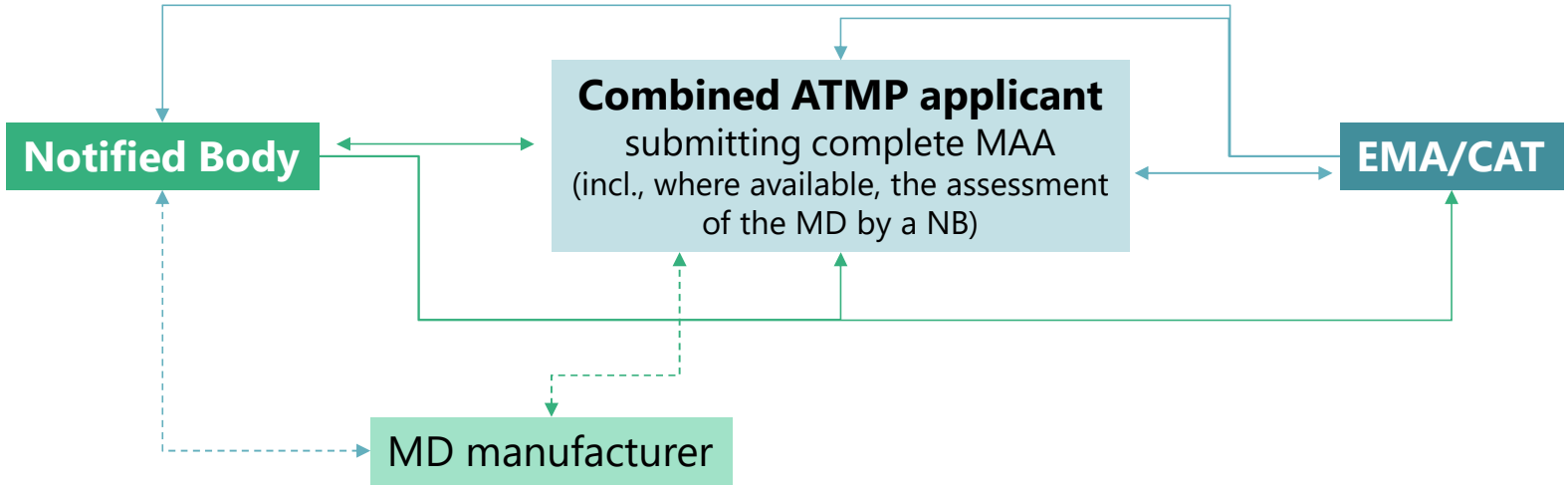

Any interaction between EMA/CAT and the NB(s) will be done in conjunction with the applicant →
Always to be involved/copied/informed.
However, for expediency, communication may be sent directly from EMA/CAT to the relevant NB.

Scenario 1: Consultation of NBs to get the <u>results of the assessment</u> of medical device(s)

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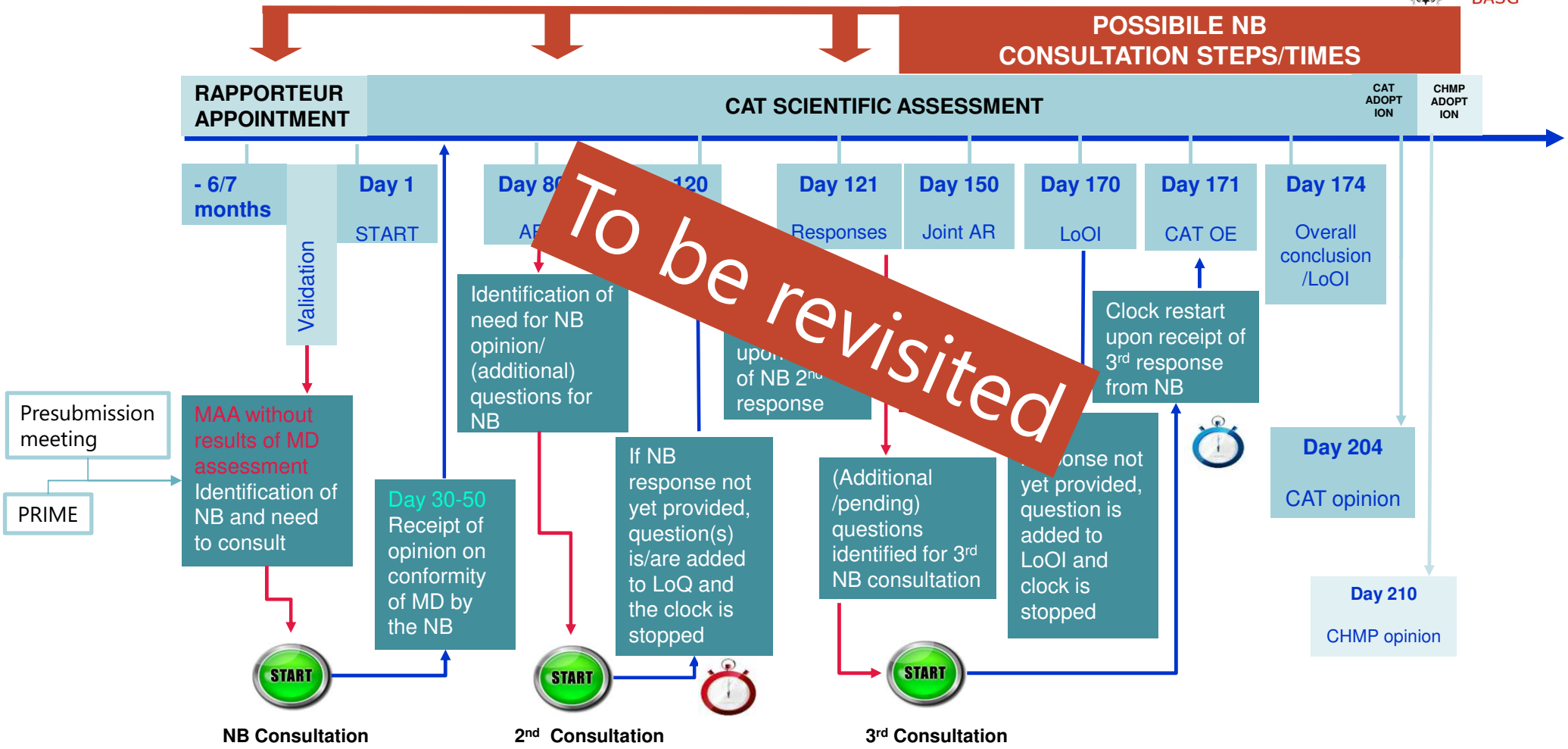

Adapted from M-H. Pinheiro/EMA 2010

Device aspects and ATMPs

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Scientific requirements

- Requirements related to medical device component(s) of combined ATMPs are detailed in ATMP specific guidelines
- Where ATMP specific guidelines do not indicate the location of the relevant information in the MAA, the principles of the "Guideline on quality documentation for medicinal products when used with a medical device" should be followed
  - Medical devices that are co-packaged with ATMPs
  - Separately obtained devices which are referenced in the Product Information, because of their potential impact on the quality, safety and/or efficacy of the ATMP
- Information on medical devices used during surgical procedures for application, implantation or administration of an ATMP which may impact on efficacy or safety as per Annex I, Part IV, Section 5.2.1 of Annex Dir2001/83/EC is expected in **Module 5**

Investigational ATMPs

Guideline on Q, NC and C requirements

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Draft guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (PDF/559.18 KB)

Draft: consultation closed

First published: 21/02/2019
Consultation dates: 21/02/2019 to
EMA/CAT/852602/2018

Work has resumed, document to be finalized

Keywords	Investigational ATMPs, gene therapy …oduct, cell therapy medicinal product, tissue engineered product, exploratory trial, first in human trial, confirmatory tri…
Description	This guideline provides guidance on the structure and …ments for a clinical trial application for exploratory and confirmatory trials with advanced therapy investigational …ducts.

www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requireme…ational-advanced-therapy_en.pdf

Medical device aspects considered

Interface activities

Not ATMP specific, but with CAT engagement

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Development → see EudraLex Volume 10

- Q&A on Complex clinical trials (May 2022)
- 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)

Marketing Authorization

- ATMP-specific Guidance documents
- Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019)
- Focus group on provision of scientific advice for medicinal product developments comprising of drug-device combinations and drug-companion diagnostic combinations
- https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices

Thank you for your attention
Questions?