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EUROPEAN MEDICINES AGENCY

Current regulatory routes for individualised therapies in the EU

Webinar on the use of platform approaches in the non-clinical and clinical domains

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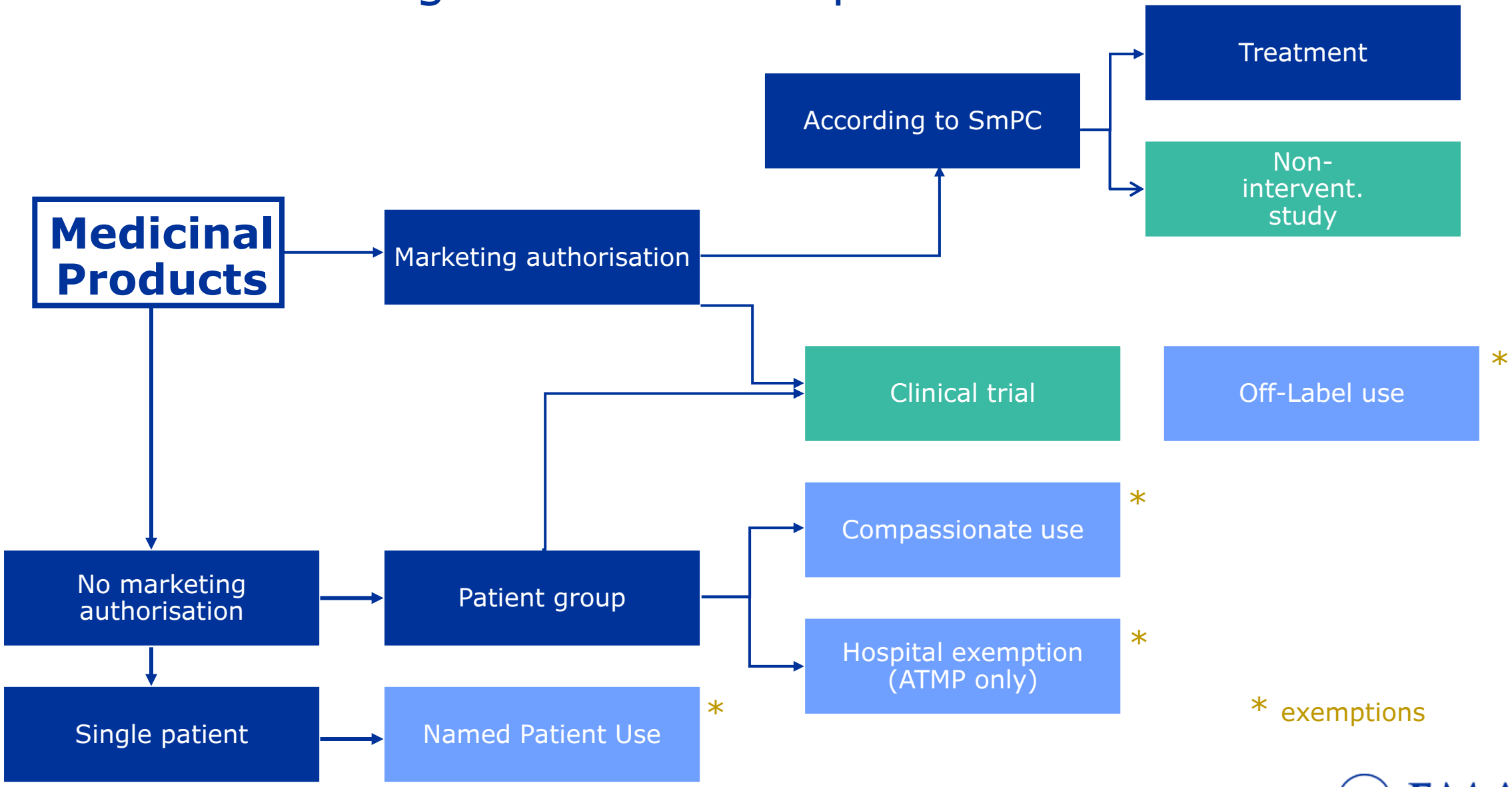
The different settings for medicinal products



Special provisions

For (yet) unlicensed medicinal products

- **„Magistrale“** and **„officinale“** - Pharmacy derogations (Dir. 2001/83/EC Art. 3.1 and Art. 3.2)

National requirements – see NCA websites

- **„Named Patient Use“** Art. 5 Directive 2001/83/EC.
  - A Member State may… exclude… medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.
- **„Compassionate use“** Art. 83 Regulation 726/2004/EC.
  - For a group of patients with chronically/seriously debilitating disease or whose disease is considered life threatening, and who cannot be treated satisfactorily by an authorised medicinal product
  - The medicinal product concerned must either be the subject of an application for a MA or undergoing clinical trials
- **„Hospital exemption“** for ATMPs only according to Art. 28(2) of Regulation 1394/2007/EC (implementing Article 3(7) of Directive 2001/83/EC).

→ **Data generated via the above provisions have limited use for registration purposes**

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„Degrees“ of personalisation…and systematic

Personalised/ individualised 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
n=1

Medicine produced without prior knowledge and unique manufacturing process and for a single patient →
True „n=1“

Only situation NOT amenable to systematic investigation
No possibility to use prior knowledge

Personalised therapy

Indication based on mechanism versus clinical symptoms

„Molecular“ indication coupled to biomarker detection → companion diagnostics

Patient specific therapy based on molecular profiling

Complexity

EU definition of personalised medicine: A medical model using characterization of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.

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N=1 therapies

But not n=1 data packages

N=1 therapies build on prior knowledge:

Example from https://doi.org/10.1038/s41573-024-01059-3

- "*In the case of milasen, the previous development of nusinersen (Spinraza; Ionis Pharmaceuticals/Biogen) for spinal muscular atrophy provided a useful template, as it established that an ASO with the same mechanism of action (modulation of mRNA splicing) and chemistry (RNA with a phosphorothioate backbone and 2′-O-methoxyethyl modifications) could be delivered by intrathecal injections, and was well tolerated*.
- Nusinersen treatment resulted in significant benefit for patients..."

Jonker, A.H., Tataru, EA., Graessner, H. *et al.* The state-of-the-art of *N*-of-1 therapies and the IRDiRC *N*-of-1 development roadmap. *Nat Rev Drug Discov* **24**, 40–56 (2025). https://doi.org/10.1038/s41573-024-01059-3

Why is „systematic“ important for clinical trials?

- Enables clinical trials
- Defines manufacturing process, determines preclinical data and clinical protocol
- Facilitates optimization of the manufacturing process
- Enables use of prior knowledge, leveraging previous results
- Supports robustness of results
- Shortens development time for following products

→ Single product name for personalised/individualised products for CTIS entry, but no formal obstacle to investigate individualised products

→ Useful to refer to earlier data in the cover letter/trial dossier, as relevant

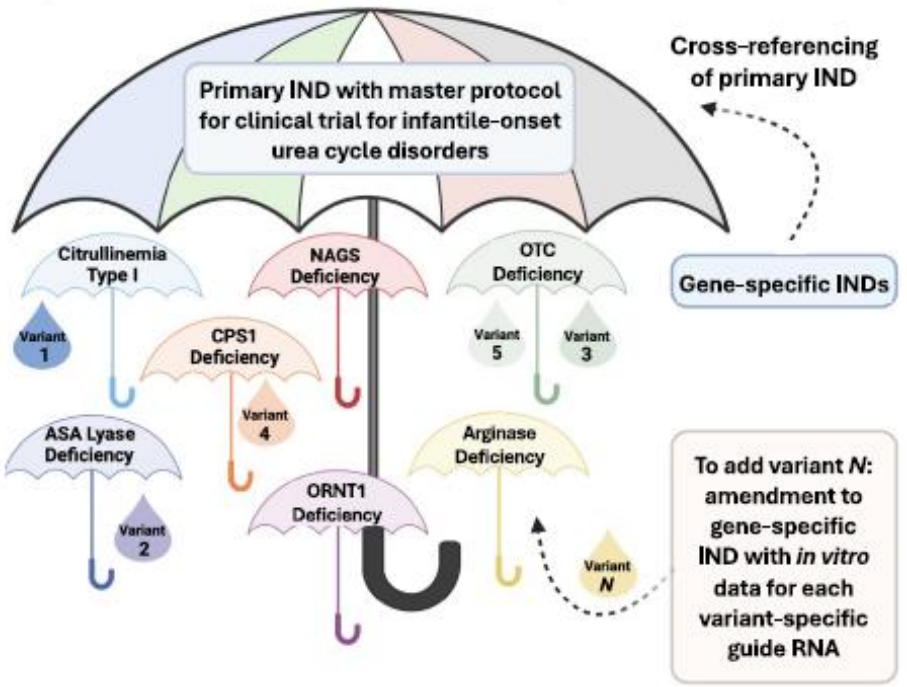
→ No formal obstacle to investigate mechanism based indications that do not fully overlap with clinical indications

So what is currently possible in clinical trials?

It is possible to test individual products in clinical trials issued from the same manufacturing process (single product name)

They can be targetting different sites on a gene → definition of the clinical indication and of endpoints

Further integration of „umbrella“ or basket possible - Complex clinical trials - Guidance elaborates on possibilities



Ahrens-Nicklas and Musunuru
How to create personalized gene editing platforms: Next steps toward interventional genetics,
The American Journal of Human Genetics (2025),
https://doi.org/10.1016/j.ajhg.2025.10.006

➡ For guidance, see EudraLex Volume 10, including complex clinical trials – Questions and answers

Leveraging prior knowledge

What is state of the art?

Irrespective of the regulatory procedure, the following principles apply:

- Leveraging prior knowledge needs to be justified by **data**
- ..including bridging **data**, as relevant
- These **data** need to be accessible to the assessor
- Publications by scientific bodies to reflect the state of the art, e.g. consensus documents, are beneficial
- Sharing knowledge may provide evidence for high level systematic scenarios, e.g. the anticipated risk of significant impact of switching the enzyme in a gene editing setting
- In CTs – provide data in the dossier with reference to their prior assessment/ acceptance in the cover letter (Earlier data only accessible to previously involved MS)

EU GMP requirements

For investigational medicinal products (IMPs)

- The manufacture of investigational ATMP must be **in accordance with GMP** (*EU GMP for ATMP*).
- The application of GMP to investigational ATMPs is intended **to protect the clinical trial subjects and for the reliability and robustness of the results** of the clinical trial.
- Follows a risk-based approach (especially in early phases of clinical trials, due to the often-incomplete knowledge about the product, as well as the evolving nature of the routines).

➢ **Manufacturing in EU**

- The manufacturing in the Union shall be subject to the **holding of an authorization**.

➢ **Manufacturing outside EU**

- **EU qualified person ‚certification' needed for import of IMPs** --> confirmation that the quality of the batch is **in accordance with the terms of the clinical trial authorization**, and manufactured in accordance **with quality standards at least equivalent to the GMP** requirements applied in the EU.
- The import of IMPs in the Union shall be subject to the holding of an authorization.

National and EMA support tools

- National Competent Authorities

- EMA

Innovation offices

Early, informal discussion for scientific and regulatory guidance on innovative medicines

National scientific advice and Simultaneous National Scientific Advice (SNSA)

Non-binding advice on CMC/Non-clinical/Clinical

Innovation Task Force (ITF)

Early, informal discussion for scientific and regulatory guidance on innovative medicines, technologies and methodologies

SME & Academia offices

Fee reductions/deferrals; tailored guidance for SMEs and non-for-profit on regulatory strategy

Scientific Advice

Non-binding advice on CMC/Non-clinical/Clinical, compliance correlated to MA success rates

Qualification of Novel Methodologies

Opinion/advice on methodologies such as biomarkers and patient registries

For more information go to Supporting innovation | European Medicines Agency (EMA)

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