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Regulatorische Rahmenbedingungen in der EU
Was macht ATMPs besonders

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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.”

- **BASG/AGES**: “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 Austrian Competent Authority.”

Warum ein “Lex specialis”

Legislation

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Regulation (EC)
No 1394/2007

Effective since
30 December 2008



10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

(1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body.

(2) Insofar as advanced therapy products are presented as having properties for treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting principally a pharmacological, immunological or metabolic action, they

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.

(5) Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector.

Cell Therapy
Medicinal Products

Gene Therapy
Medicinal Product

Tissue Engineered
Products

Combined ATMPs

Besonderheiten von ATMPs

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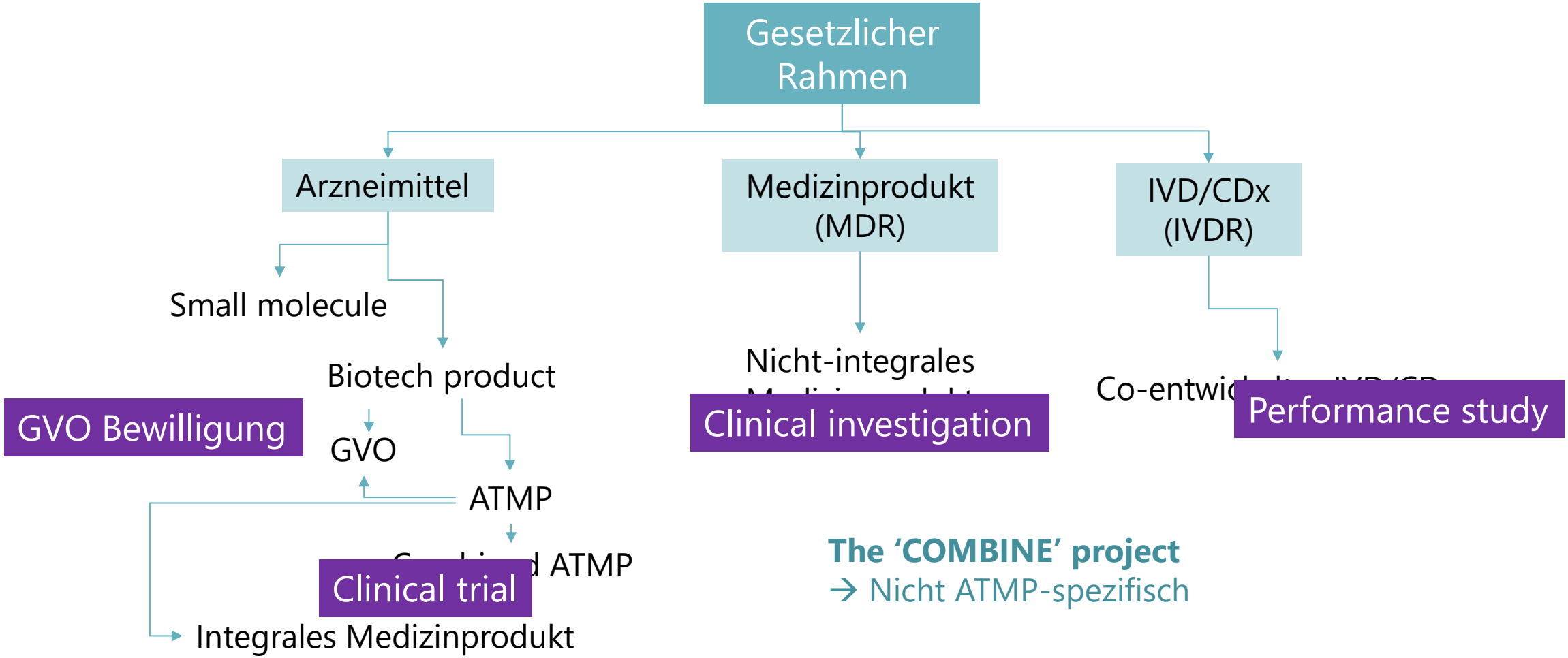
- Generelle Anforderungen gelten: quality, safety, efficacy; Klinische Prüfung, Zulassung
- Risk-based approach → Notwendige Daten berücksichtigen Natur des ATMP
- „The process is the product" → Notwendigkeit produkt-spezifischer Daten; KEINE generischen Ansätze!
- Schnittpunkt von Gesetzgebungen → Komplexität

- Meist seltenen Indikationen (in Kindern) ohne Behandlungsalternativen
- Potenziell langanhaltende Wirkung – langanhaltende unerwünschte Wirkung
- Langzeitfolgen können erst mit der Zeit erhoben werden – Long term follow up 15Y
- Verblindungs(un)möglichkeit, Kosten, ...
- Erstattung: Notwendigkeit der Begründung des Benefits über bestehende, chronische Behandlungsmöglichkeiten

Welche Anforderungen können zutreffen?

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Arzneimittelperspektive



The 'COMBINE' project
→ Nicht ATMP-spezifisch

https://health.ec.europa.eu/medical-devices-topics-interest/combined-studies_en

ATMPs und Medizinprodukte

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Nicht alle ATMP-MP Kombinationen sind “combined ATMPs“

Combined ATMP according to ATMP Regulation definition

- ATMP has one or more **integral** medical devices (MDs) or active implantable MD components in scope the EU medical device legislation as part integral part of the product

example: Alginate encapsulated porcine pancreatic islet cells

ATMP with an integral medical device

- Integral device, but combined ATMP definition not fulfilled

example: viral vector in a prefilled syringe

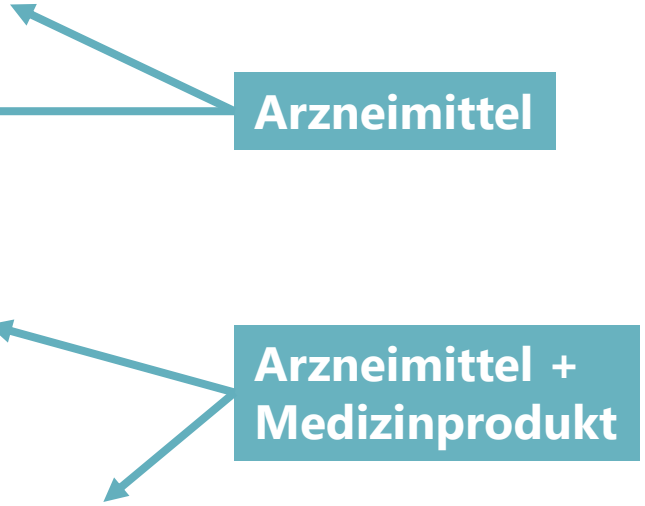
ATMP with a non-integral device (co-packaged)

- Medical device(s) for administration, correct dosing or use

example: ATMP with a refillable co-packaged delivery device

ATMP to be used with a referenced medical device (← SmPC)

example: ATMP to be used with a specific surgical tool, e.g. dedicated catheter



Guideline on Q, NC and C requirements for investigational ATMPs in clinical trials – with CTCG (CT Coord. Group)

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Current version

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

Adopted
Reference Number: EMA/CAT/22473/2025
Legal effective date: 01/07/2025

English (EN) (745.23 KB - PDF)
First published: 06/02/2025
View



- Multidisciplinary guideline on development, manufacturing and quality control, non-clinical and some clinical aspects for investigational ATMPs - intended as stand-alone document
- Guidance is by principles rather than "cooking recipes" – due to ATMP heterogeneity
- Requirements for clinical trials and guidance towards marketing authorization (MA)
- Scientific characteristics as structural principle → "cell-based" products" and "gene therapy" → Joint text, but split where needed
- Differentiation into exploratory/confirmatory trials rather than phases

Finding the balance – in rare disease/ATMPs

And ensuring trial participant safety

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- Push for innovation
- Develop quickly - milestones
- Unmet medical ne
- Phase-appropriat
- Immature processes
- Frequent manufacturing changes
- Clinical data need to relate to specific product profile
- Financial pressure

- No short-cuts in patient safety
- Products not well-characterized
- Limitations of preclinical models
- Uncertainties about efficacy early on
- impact on the recipient?
- s (paediatric)
- dosing of the same product or related products
- Accelerated development → early, pivotal data

Entwickler müssen bei Akzelerierung die Relevanz der Daten in Betracht ziehen

ATMPs und Personalisierung

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Personalised/ individualised medicine

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. individual RNA approaches (colloquial) **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

„Molecular“ indication with a predictive biomarker → companion diagnostic (CDx)

Patient specific therapy based on molecular profiling (therapeutic practice)

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.

What is the next „big Thing“?

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Gene Editing

- *Ex vivo* oder *in-vivo*
- Diverse experimentelle Ansätze
- Gemeinsamkeiten:
  - Effizienz des on-target Effekts
  - Häufigkeit und Risiko von off-target Effects
  - Risiken durch das Transportvehikel, e.g. Virus, Lipid Nanoparticle, etc
  - Analytischer Ansatz und Sensitivität
- Wunsch nach Guideline vs. Geringe Erfahrung
- CAT Arbeitsgruppe für ein Question and Answer Document zu Gene editing
- Workshop 2027

Warum gibt es mehr zugelassene ATMPs in den USA?

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- Höhere Zahl an Anträgen
- Breitere Definition von Zell-und Gentherapie
  (z.B allogene Stammzellen sind in Europa in der Zell- und Gewebegesetzgebung)
- Zulassung auf Basis geringerer Anforderungen
  - **USA**: „reasonable expectation“ of positive benefit risk; surrogate parameter für accelerated assessment; zusätzliche Flexibilität
  - **EU**: „demonstration“ of positive benefit risk auch für Conditional Marketing Autorization (MA); MA under exceptional circumstances, wenn Bedingungen zutreffen
- Preisverhandlungen/Health Technology Assessment

Zusammenfassung

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- Innovativer Bereich mit rascher Entwicklung und teilweise geringen Erfahrungswerten
- ATMPs sind Biologika, generisches Denken unangebracht
- ATMPs werden für Patienten entwickelt, deren Sicherheit ist wesentlich → Einhaltung der Qualitätsstandards auch bei der Risk-based approach
- Immanente Herausforderungen
- Keine reduzierten Standards bei seltene Erkrankungen, unmet need, oder für vulnerablen Gruppen, aber realistischer Zugang
- Die ATMP Entwicklung ist generell akzeleriert → Druck auf effiziente Entwicklung regulatorische Kompetenz und post-marketing Anforderungen →
- Notwendigkeit ein positives Benefit Risk bei der EU Zulassung zu belegen
- Frühe Interaktion mit Behörden empfehlenswert!

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)

Classified as public by the European Medicines Agency

Danke für Ihre Aufmerksamkeit
Fragen?

