Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

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Regulatory aspects in the development of ATMP - questions and answers

Regulatorische Aspekte bei der Entwicklung von ATMP – Fragen und Antworten

SaxoCell Clinics Workshop - Klinische Studien mit ATMP
16. März 2023

Bettina Ziegele

Disclaimer

The views expressed in this presentation are the views of the author.

Decisions are made while considering individual cases on scientific grounds.

Neither the Paul-Ehrlich-Institut nor its experts obtain any finances from industry developing medicinal products.

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Regulation – „It's a giving & taking"

- Overview of the PEI
- Advanced Therapy Medicinal Products (ATMP)
- (Regulatory) development of ATMP
- Regulatory support alongside pharmceutical development
- Some fact & figures

Tasks and responsibilities of the PEI

Support and expertise

- Regulatory and scientific advice
- Annual reports for blood and tissues products
- Research in the areas of PEI's responsibilites, e.g. gene therapy medicinal products, viral vaccines

Authorization procedures

- Approval of clinical trials
- Granting of national authorisations
- Assessment of applications for marketing authorisation in European procedures

Testing and surveillance

- Official testing and release of batches
- Inspections GMP/GCP (national and European)
- Pharmacovigilance

Biological Medicinal Products

- Definition: Annex I of Directive 2001/83/EC:

biological medicinal product : **active** substance = **biological** substance

biological substance = substance produced by or extracted from **biological source** &

⇩

characterisation and determination of quality by
physico-chemical-biological testing, production process and control

⇩

Uncertainty of future scientific development of methods for characterisation, production process and control

Basis for classification: current state of the art

Biological Medicinal Products
Regulation EC 726/2004 – Annex

- Immunological medicinal products
- Medicinal products derived from human blood and plasma (…)
- Medicinal products developed by biotechnological processes*

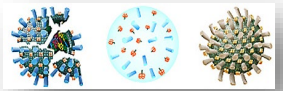
*Recombinant DNA technology, controlled expression of genes…, Hybridoma and monoclonal antibiotic methods

- Advanced Therapy Medicinal Products

…are authorised by the community (i.e. centralised procedure)

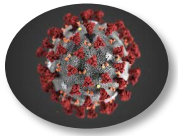
Medicinal products in PEI responsibility

Vaccines



Human & veterinary

Vector- & DNA/RNA-vaccines

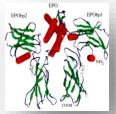


COVID-19 vaccines

Antibodies, proteins & allergens

Monoclonal antibodies (MAB)

Antibodies

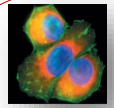


Blood products

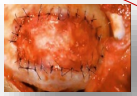
Allergens

Stem cell & tissue preparations & ATMP

Haem. stem cell-transplantation

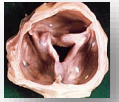


ATMP*



Somatic cell (SCT) & gene therapy medicinal products (GTMP)

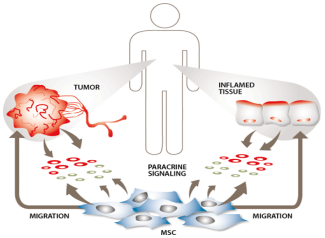
Tissue engineered Products (TEP)



Tissue preparations

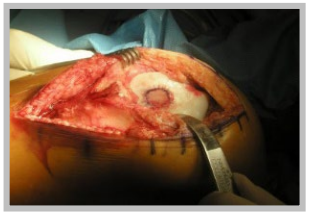
*Advanced Therapy Medcinal Products

Advanced Therapy Medicinal Products - ATMP



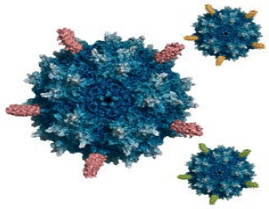
SCT

Cell-based therapeutic vaccines



TEP

Ceratinocyte sheets



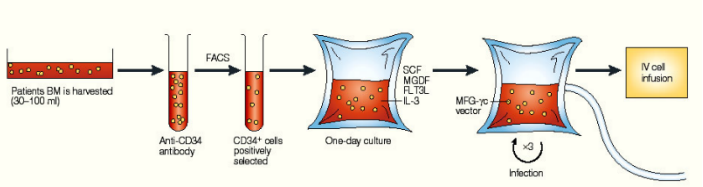
GTMP

Plasmid tumor vaccines

Combined ATMP

Encapsulated islet cells

Reg. (EC) No.1394/ 2007



Gene therapy medicinal product (GTMP)

Gene therapy medicinal product (GTMP) = biological medicinal product

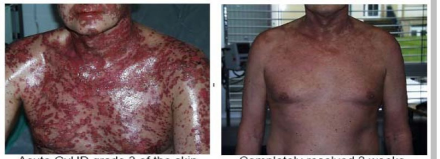
➡ characteristics:

N.B.:
Vaccines against infecious diseases ≠ GTMP

substance contains or constists of a **recombinant nucleic acid,** or is used in or administered to human beings **to regulate, repair, replace, add or delete a nucleic acid sequence**

and

therapeutic, prophylactic or diagnostic effect directly **related to the recombinant nucleic acid** it contains or to the product resulting from the expression of that sequence


Acute GvHD grade 3 of the skin

Completely resolved 3 weeks after the administration of MSC

Tissue engineered product (TEP)

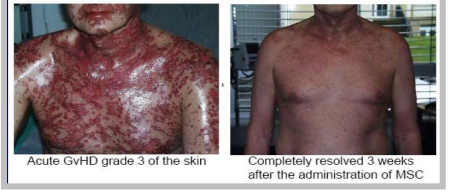
Tissue engineered product (TEP)
= biological medicinal product
➡ characteristics:

- contains or consists of **engineered** cells or tissues

and

- is presented as having properties for, or is used in or administered to human beings with a view to **regenerating, repairing or replacing** a human tissue

≠ TEP:
Products containing or consisting exclusively of **non-viable** human or animal **cells and/or tissues**, which do **not contain any viable cells or tissues** and which **do not act principally by pharmacological, immunological or metabolic action.**


Acute GvHD grade 3 of the skin

Completely resolved 3 weeks after the administration of MSC

Tissue engineered product (TEP)

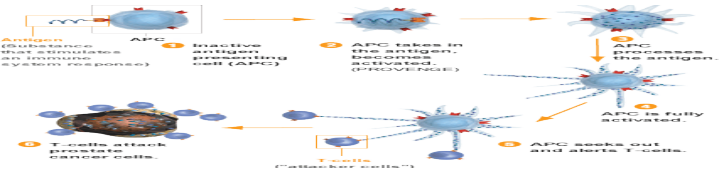
Cells or tissues = **'engineered'** if

N.B.
The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations.

the cells or tissues have been subject to **substantial manipulation**, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved

or

the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor (**„non-homologous use"**).



Somatic cell therapy medicinal product (SCT)

Somatic cell therapy medicinal product (SCT) = biological medicinal product

➡ characteristics:

N.B.
The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations.

consists of **substantially manipulated** cells or tissues:
biological characteristics, physiological function or structural properties, relevant for the intented clinical use have been altered

or

consists of cells or tissues that are not intended to be used for the same essential function or functions in the recipient as in the donor (**„non-homologous use“**)

and

is presented as having properties for, or is used in or administered to human to obtain a **therapeutic, diagnostic or preventive effect** through **metabolic, pharmacological and immunological** means

Manipulations

Manipulations according to Annex I: **not** considered as substantial manipulations:

— cutting,
— grinding,
— shaping,
— centrifugation,
— soaking in antibiotic or antimicrobial solutions,
— sterilization,
— irradiation,
— cell separation, concentration or purification,
— filtering,
— lyophilization,
— freezing,
— cryopreservation,
— vitrification.

Examples for substantial manipulations:

— changes of tissue (e.g. encymatic digestion)
— cultivation,
— expansion,
— genetic modification

and

- basically those procedures not listed.

Combined ATMP

Combined advanced therapy medicinal product

➡ conditions:

integral part of the product: one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC **or** one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC

and

its cellular or tissue part must contain **viable** cells or tissues

or

its cellular or tissue part containing **non-viable cells or tissues** must be liable to act upon the human body with **action** that can be considered as **primary** to that of the devices referred to

SCT, TEP and GTMP – some examples

1. SCT:

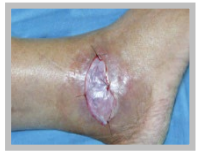
- **Pankreas islet cells:**
  type I-Diabetes
- **Immunotherapeutics / cell-based therapeutic vaccines:**
  bronchial carcinoma

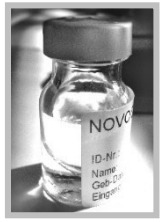
2. TEP:

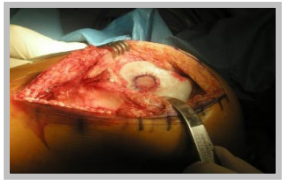
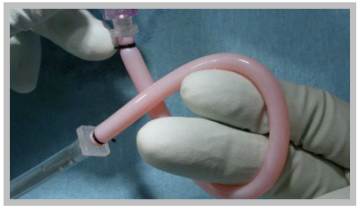
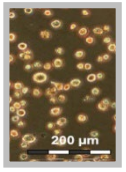
- **Autologous chondrocyte transplants:**
  reconstitution of bones and cartilage defects
- **Ceratinocyte sheets (allogeneic+autologous):**
  burns, ulcers, plastic surgery
- **Products derived from mucosal cells:**
  reconstruction of urethra, repair of cornea

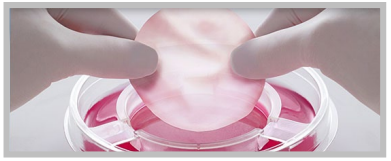
3. GT:

- **Genetically modified mesencymal stem cells (allogeneic):**
  makuladegeneration
- **plasmid tumor vaccine:**
  ovarialcarcinoma



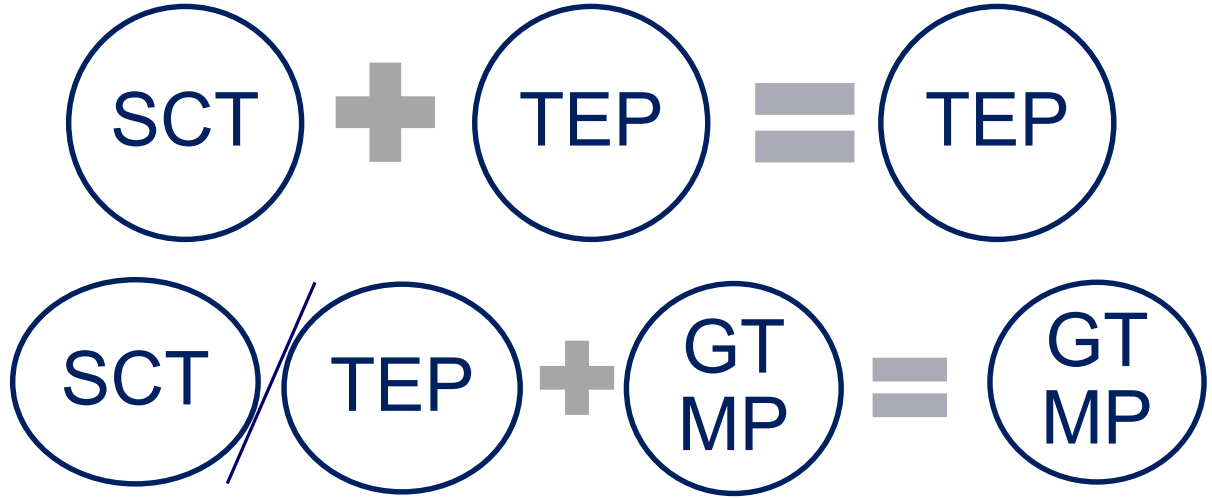


What if….

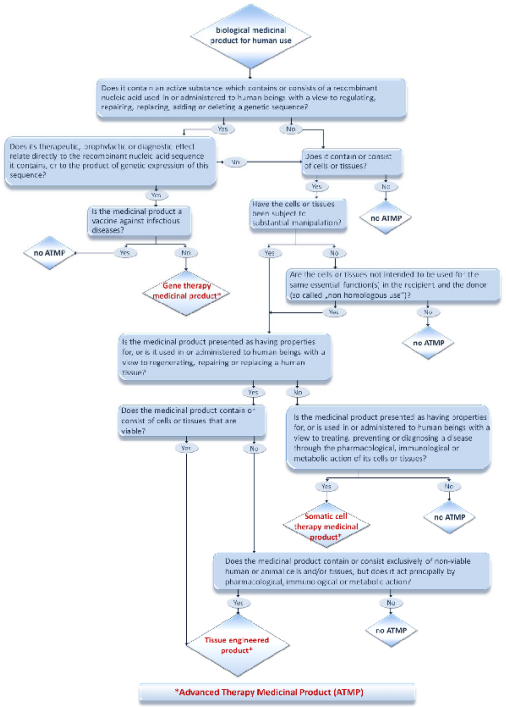
… a product which may fall within the definition of



… or it…

… contains viable cells or tissues:
the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.

Decision tree for ATMP



ATMP **development**

- proof of concept
- biodistribution
- first starting dose
- target organs of toxicity and biological activity
- safety monitoring in phase I
- patient selection

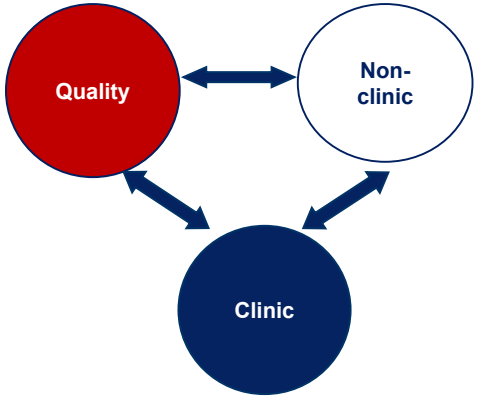
benefit/risk ratio phase I

GUIDELINE ON THE NON-CLINICAL STUDIES REQUIRED BEFORE FIRST CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

ATMP – What is special?

! New therapeutic development
! Highly innovative
! Complex
! Individualised
! Specific manufacturing



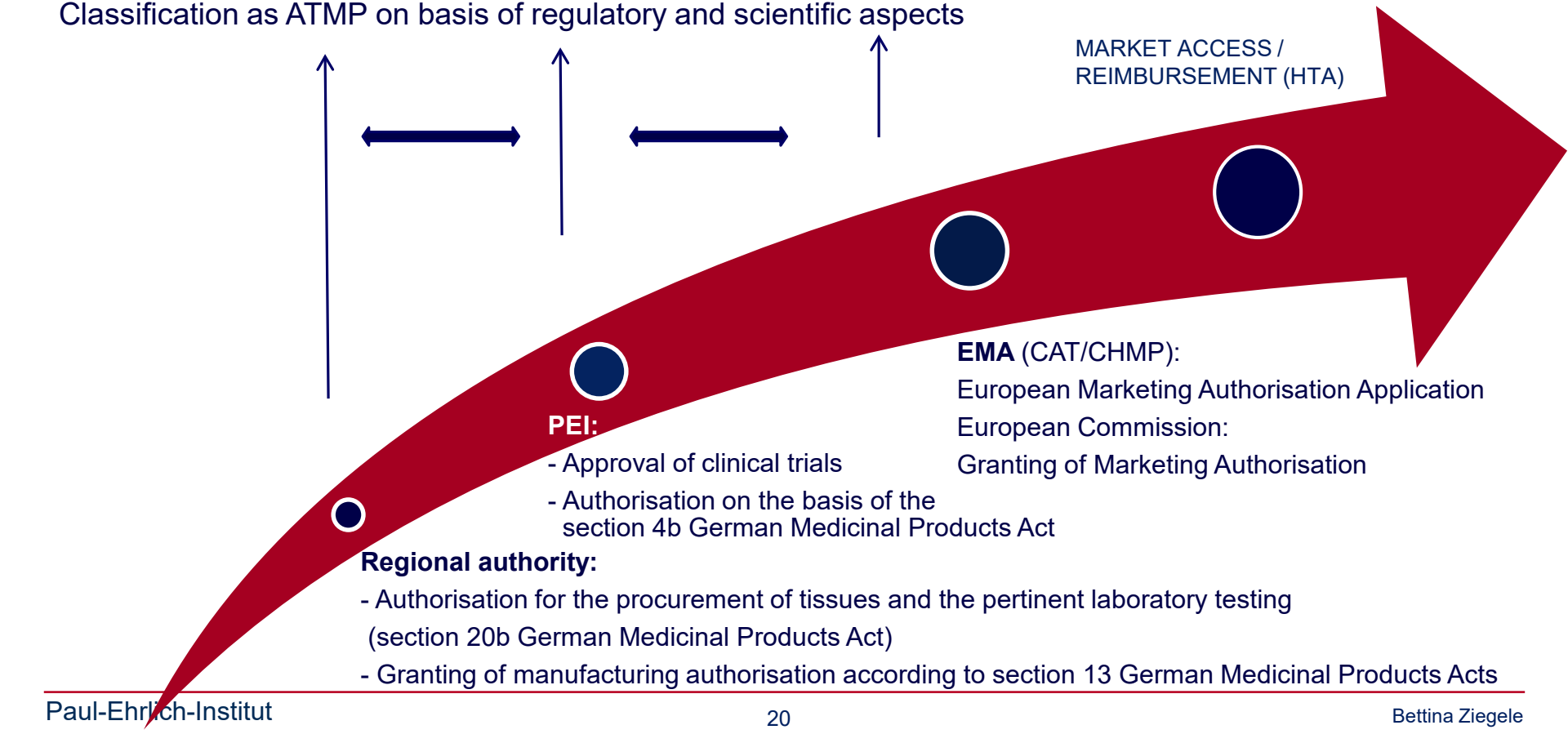
„One process – one product“ – paradigm:
Changes in pharmaceutical quality:
new non-clinical testing???!!!

Quality and non-clinic/clinic are intrinsically linked

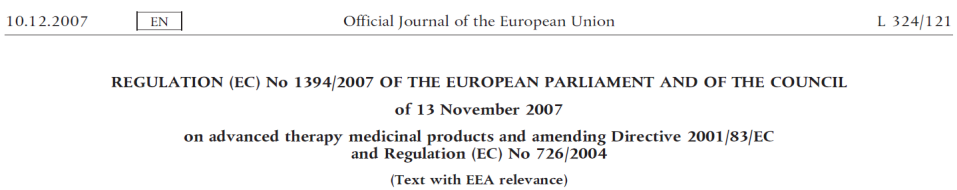
Biotechnological medicinal products are „individuals“

Regulatory development of an ATMP

Classification as ATMP on basis of regulatory and scientific aspects



Legal aspects of ATMP



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

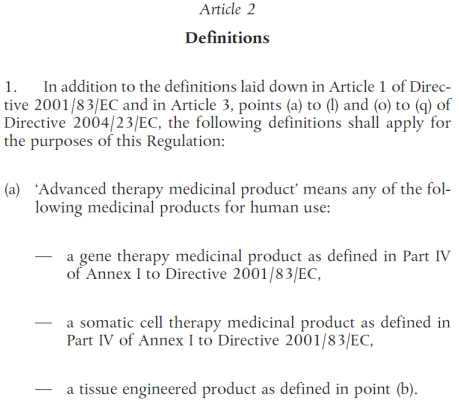
(Text with EEA relevance)

Article 28 of the Regulation ⟶

National regulation „Hospital Exemption“

National implementation in Germany ⟶

Section 4 b (sub-section 3) of the **German Medicinal Products Act**



Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

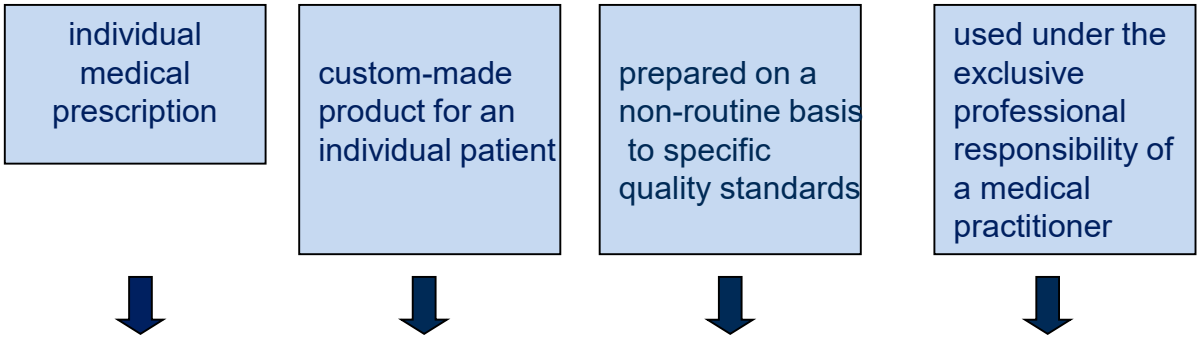
— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

Hospital Exemption

scope pursuant to article 28 regulation (EC) no 1394/2007

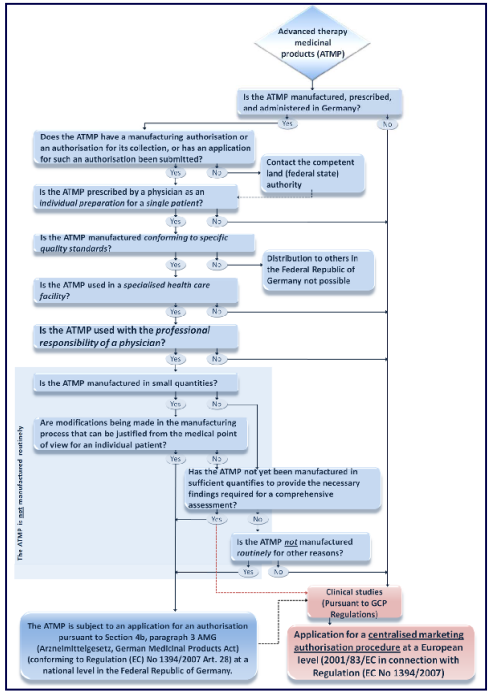


Prepared on a non-routine basis are, in particular, medicines:

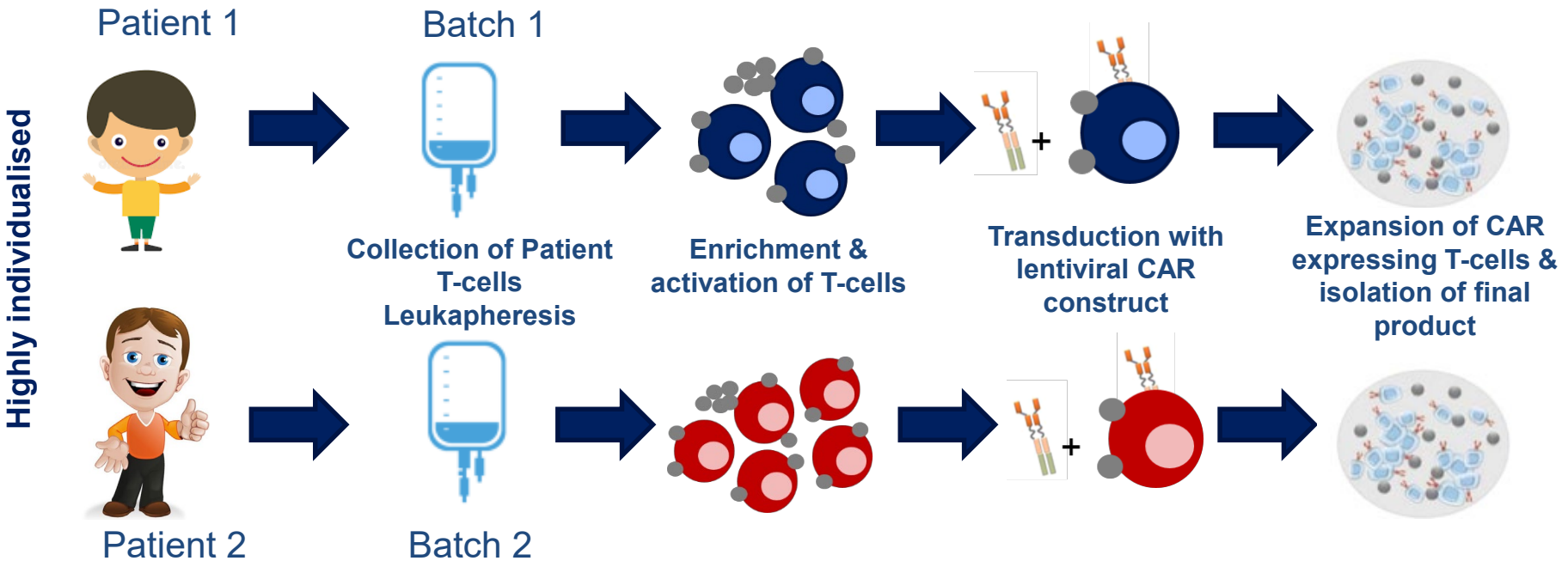
1. which are manufactured **in small quantities**, and in the case of which, based on a routine manufacturing procedure, variations in the procedure which are medically justified for an individual patient, are carried out, or

2. which have **not yet** been manufactured in **sufficient quantities** so that the necessary data to enable a comprehensive assessment are not yet available.

Decision tree for section 4b AMG (German Medicinal Products Act)

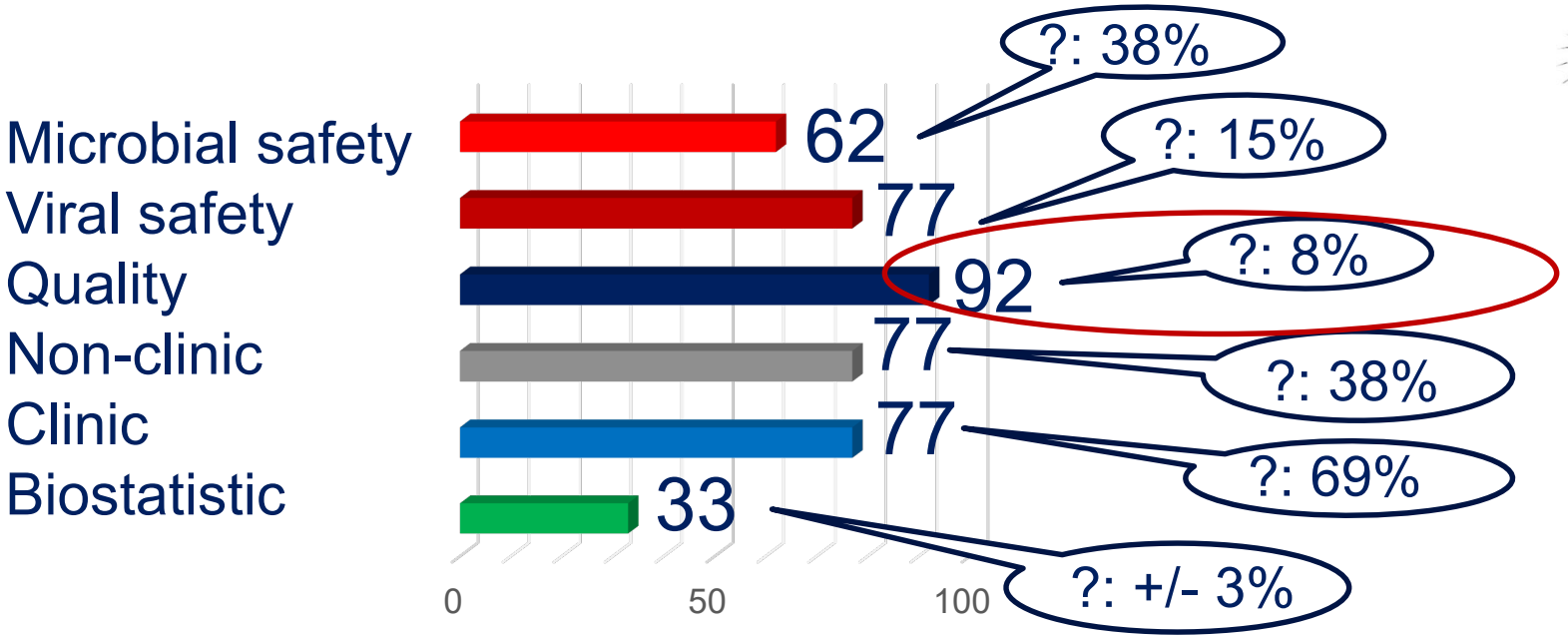


CAR-T-cells: an example for specific manufacturing



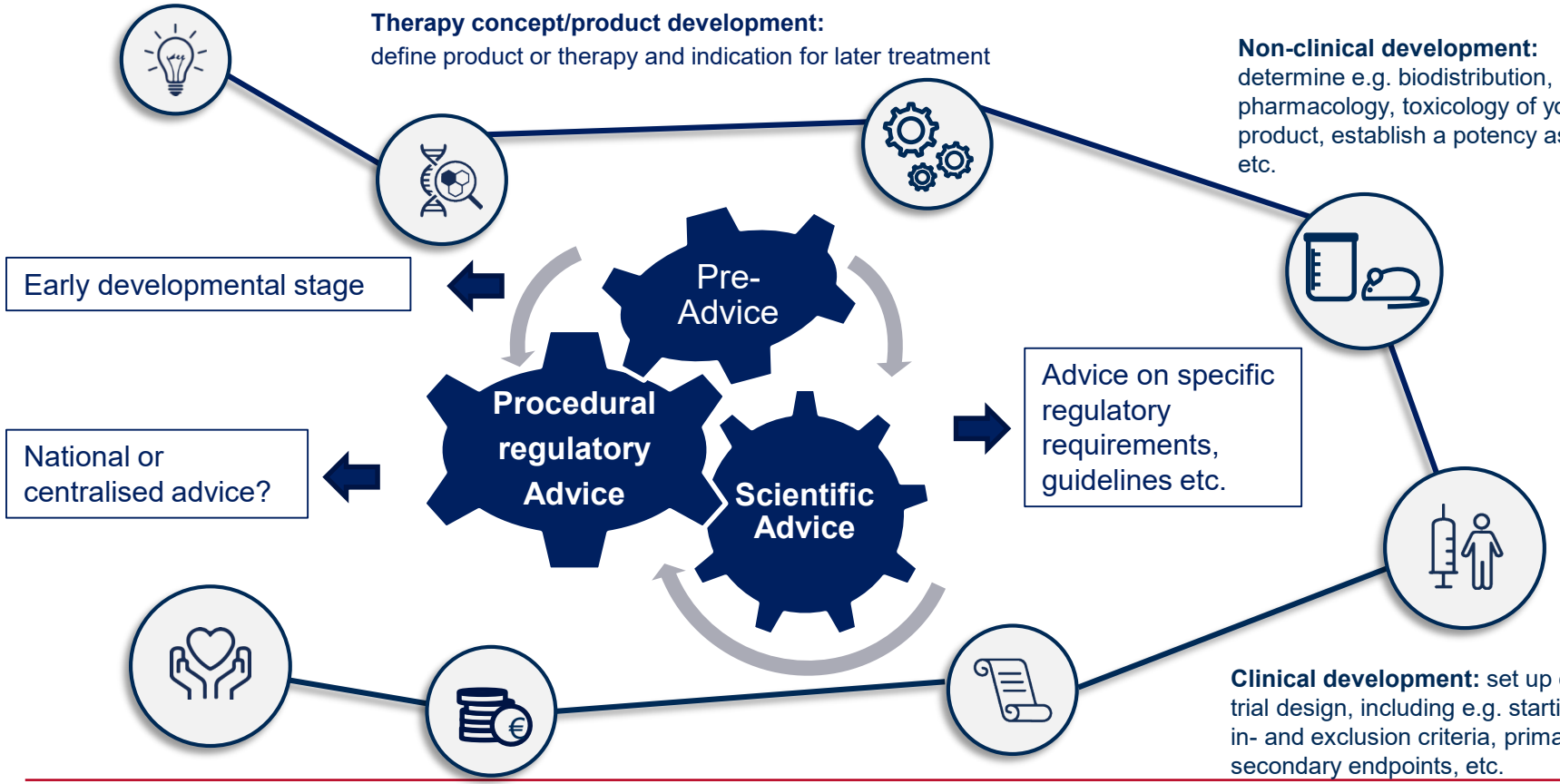
- Same specification - complexity in production and quality - consistency of (end) product(s)

Major objections in Clincial Trial Applications for ATMP



?: Questions in Scientific Advice

From bench to bedside – development & advice



PEI: areas of expertise

Scientific Expertise

Immunology:
Therapeutic Vaccines

Haematology / Transfusion Medicine:
Stem cell preparations (non-homologous use)

Medical Biotechnology:
Advanced Therapy Medicinal Products (ATMP)

Tissue Engineering, Somatic Cell Therapeutics

Gene Transfer Medicinal Products

Supporting Units

- Microbial Safety
- Viral Safety
- Biostatistics
- Clinical Trials
- Pharmakovigilance
- Legal Affairs
- EU-Cooperation

Pre-Advice

Pre-Advice **Free of charge!**

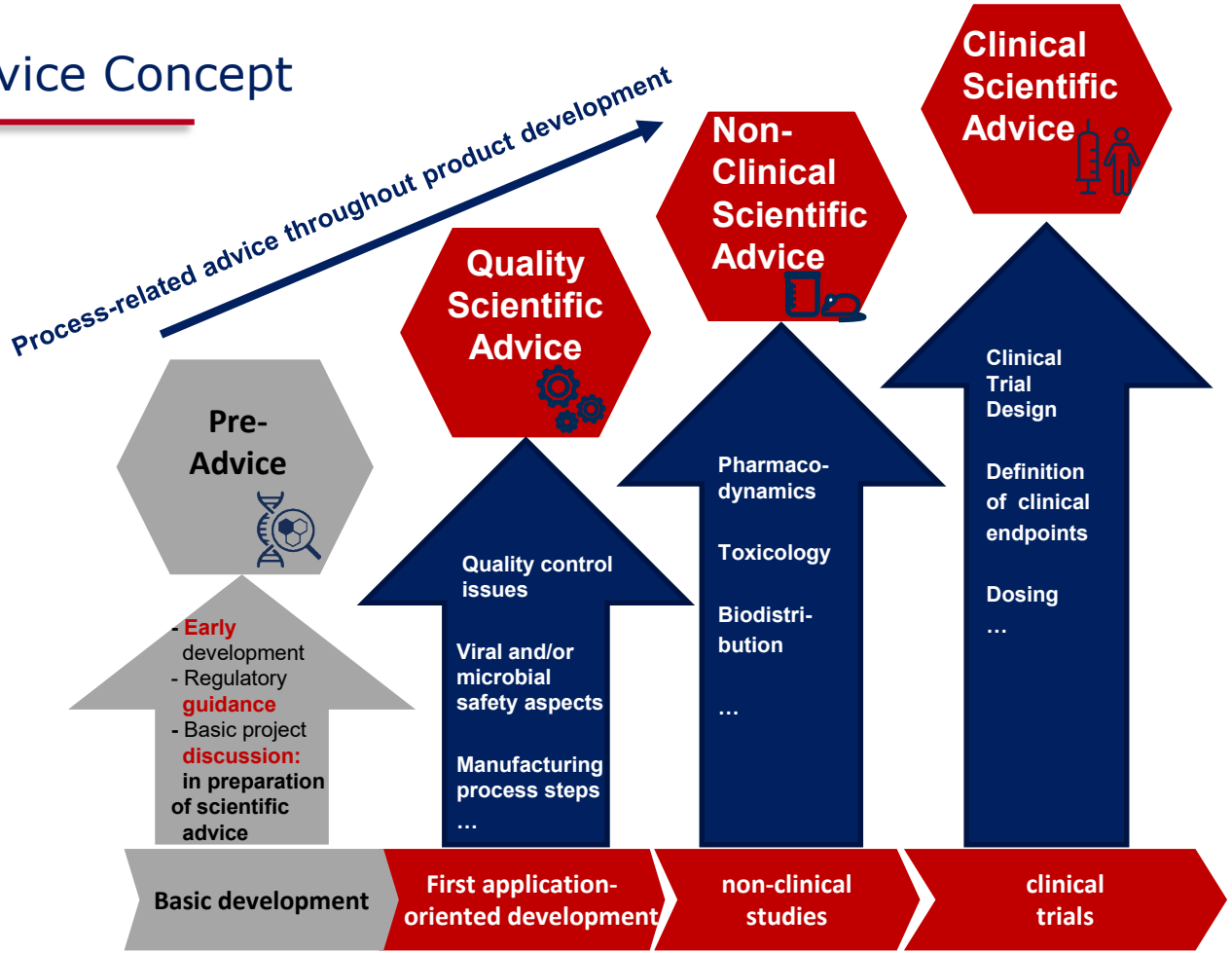
- At a very early stage of development
- Get basic orientation on regulatory aspects of development
- Exchange informally with experts on general issues
- Prepare for a national scientific advice meeting

National Scientific Advice

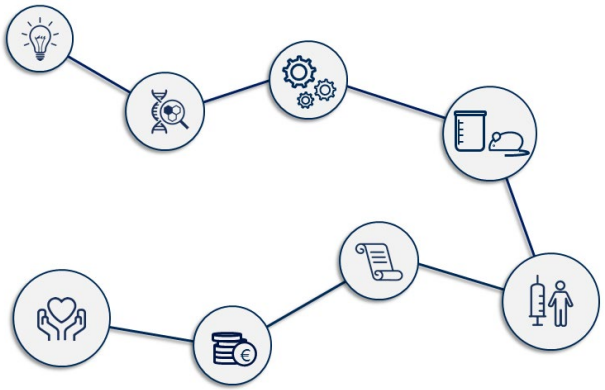
National Scientific Advice

- Receive procedural and regulatory advice
- Get answers on quality, non-clinical and/or clinical issues
- Discuss specific project and product related aspects

Stepwise Advice Concept



PEI Support



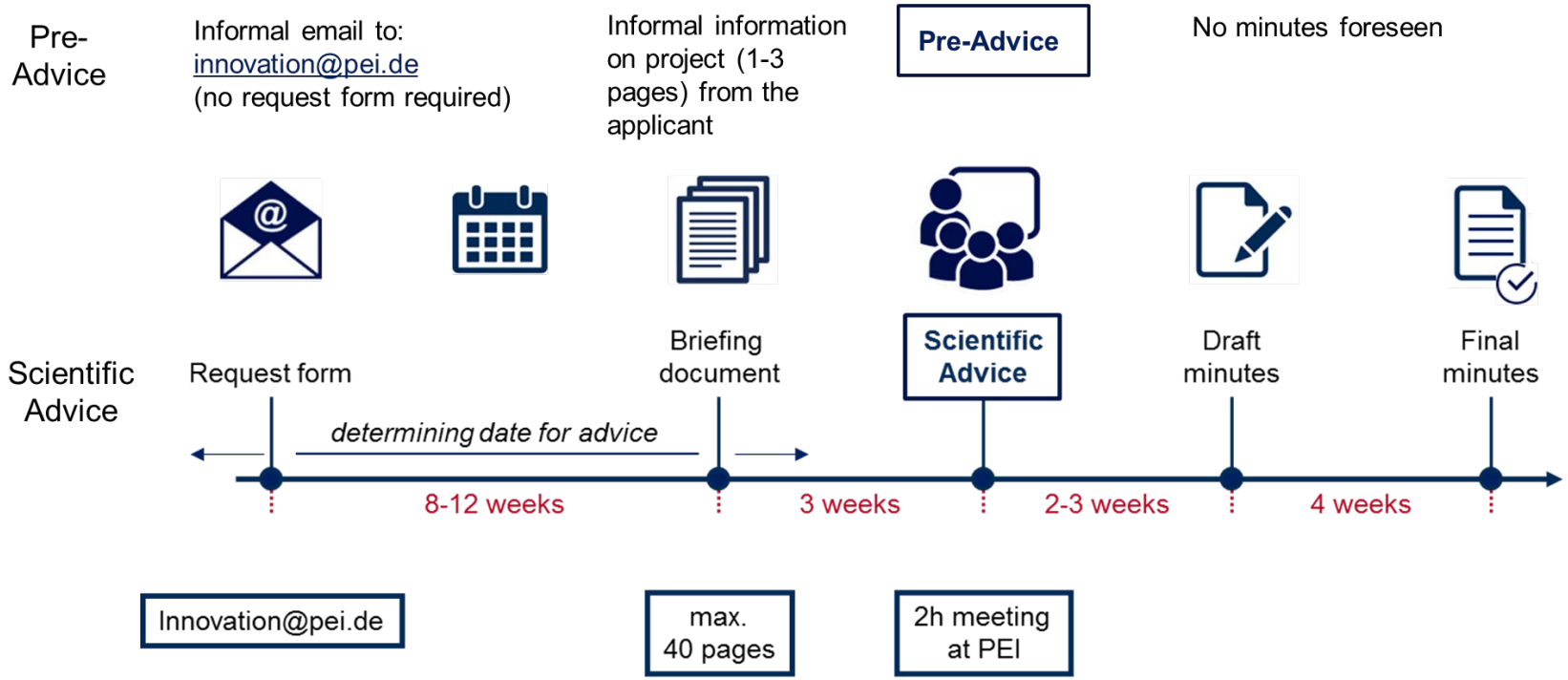
Our offer:

- We provide tailor-made regulatory and scientific advice meetings
- We encourage open discussion on scientific aspects within the relevant regulatory framework
- We support all developers of medicinal products

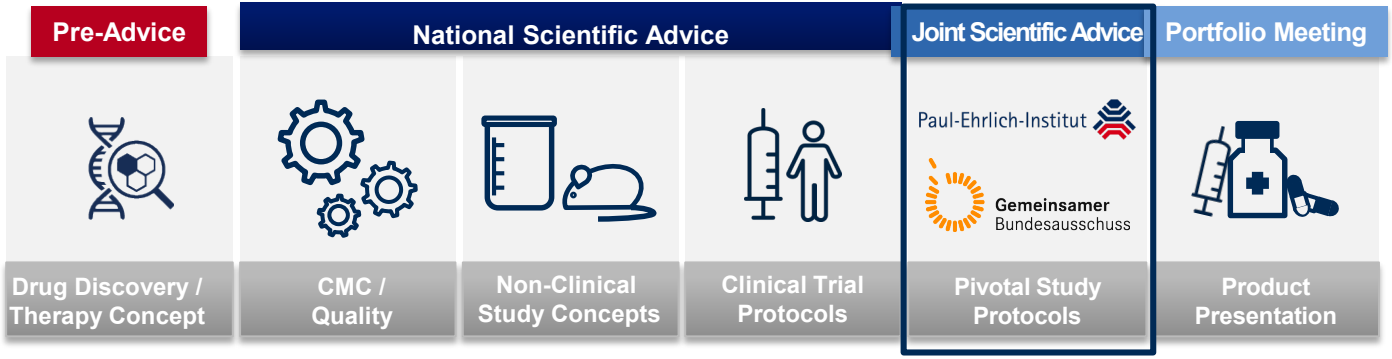
Your benefits:

- You will learn about the regulatory and legal environment of your development
- You will profit from discussion with European specialists in biomedicine
- You will be best prepared for clinical trial applications

Pre-/Scientific Advice procedure at the PEI



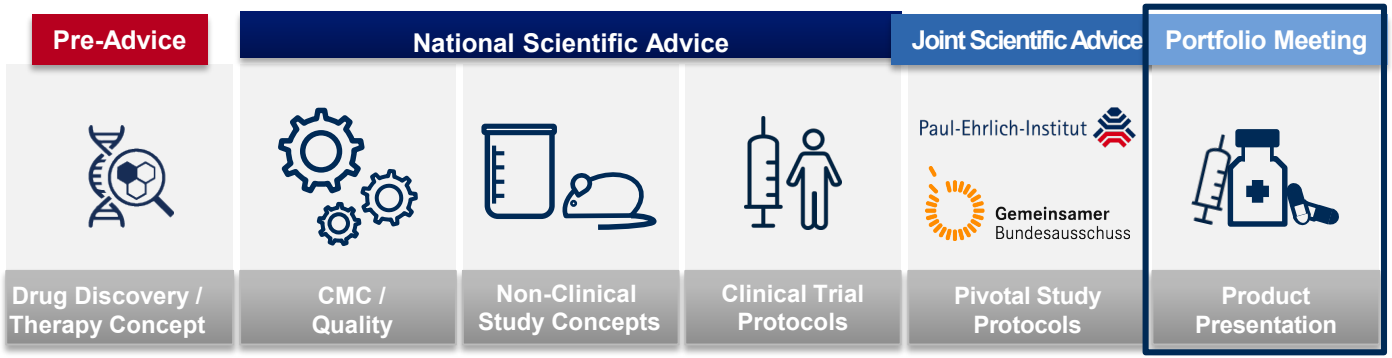
Joint Scientific Advice



Joint Scientific Advice

- When preparing for a pivotal study
- Exchange with the PEI & the Federal Joint Committee (G-BA)
- Discuss regulatory and benefit assessment related aspects

Portfolio Meeting



Portfolio Meeting

- Presentation of medicinal products in development
- Information about product pipeline in advance of CTA

SNSA pilot phase 2 – the way to optimization

1st NCA coordinating

2nd NCA participating

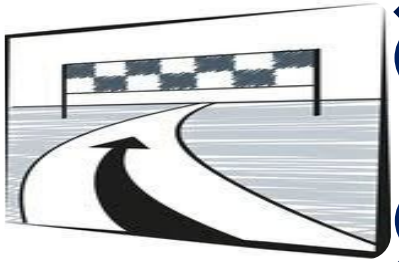
+ optional in *observing role:*

Additional NCA

3rd NCA participating

CTCG representative

Applicant



- Single entry point @: SNSA@pei.de, common application form & briefing book
- Harmonised process and predictable timetable:
  (fixed timelines at start of procedure & flexibility under special circumstances)
- Clearly documented outcome of position of each NCA in meeting report

SNSA addressees & topics

Target groups

-**no restrictions**:
all types of applicants can apply

Focus on **innovative developments**, but not only…

- especially requests for **advice in early stage of development +**

- special guidance for **SME[+]** **and academia**

Scope

Scientific & regulatory advice

Questions on e.g. **quality, safety and efficacy**

- focusing on **early stage of product development**

- including, but not restricted to clinical trial applications/concepts, e.g. multinational trials in small (patient) populations

Restrictions:

- Requests for **combination products** for human use only accepted if within remit of participating NCAs

- **HTA*** and reimbursement aspects **currently excluded**

- Limitation of SNSA to the **scope and questions** raised in the **briefing documents**

[+] Small and Medium Size Enterprise

*Health Technology Assessment

SNSA timelines

Submission of the application to SNSA@pei.de

Deadline* for applicant to submit the briefing package including the list of questions to the NCAs (if not yet sent to the Coordination Unit) and fees payment (if payment in advance is requested)

Deadline for applicant to submit draft minutes template to the lead NCA

Applicant: option for clarification request

max. day -30 | max. day -5 | max. day 65 | max. day 90 +

0 – 5 days | 0 – 5 days | 0 – 30 days | 0-20 days | 0-5 days | 0-10 days | 0-15 days | 0 – 5 days | 0 – 5 days

Day -10

Coordinating Unit: confirmation of SNSA meeting date & lead NCA to the applicant & the NCAs involved

Day 0

START OF PROCEDURE

Lead NCA: send the SNSA meeting link & the template for the minutes to the applicant and the participating NCAs

Day 55

SNSA MEETING

Day 85

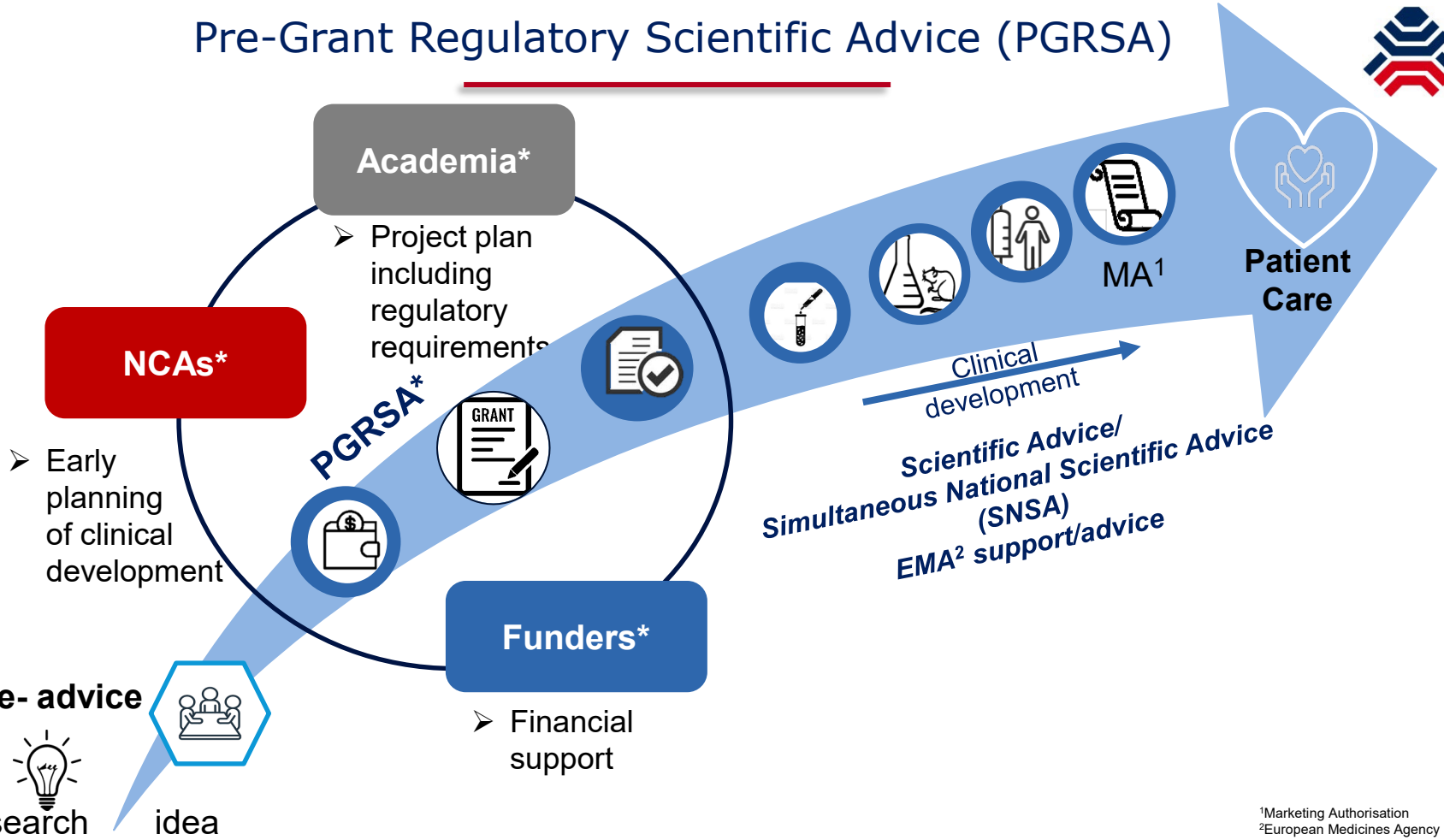
Comments on draft minutes from the participating NCAs to the lead NCA

Day 90

Lead NCA: review final report & send it to the applicant together with the feedback survey for completion

*adapted to changed requirements

Pre-Grant Regulatory Scientific Advice (PGRSA)



[1]Marketing Authorisation
[2]European Medicines Agency

Overview EMA support

ITF[1] - Briefing Meetings	ATMP Certification
Scientific Advice	ATMP Classification
Orphan Designation (Protocol Assistance)	PRIME [2]

[1] Innovation Task Force
[2]Priority medicine

ITF (Innovation Task Force) -Meetings

- Emerging therapies and technologies
- Multidisciplinary group of EMA committees and working parties
- Scope: scientific, regulatory and legal
- Advice on procedures for e.g. characterisation of medicinal product

- Free of charge
- Forum for early dialogue of medicines innovation
- Informal exchange

- Additional information: ITF-Meetings
- itfsecretariat@ema.europa.eu for human medicines, or
- tfvet@ema.europa.eu for veterinary medicines.

Orphan Designation

- Life-threatening or chronically debilitating disease
- Less than 5 in 10.000 patients or high investment relative to return
- No existing diagnosis, prevention, or treatment/signifikant benefit

- Protocol assistance free of charge for Academia and SMEs
- Evaluation process takes max. 90 days
- Independant of developmental stage
- Not legally binding

- Additional information: Orphan Designation
- orphandrugs@ema.europa.eu

Scientific Advice

- Based on recommendation of SAWP (Scientific Advice Working Party = pool of experts of NCAs)
- Focus on development strategies rather than pre-evaluation of data!
- Preparing for CHMP* opinion on product development with view to Marketing Authorisation

- Independent of developmental stage
- Parallel Scientific Advice with FDA [1] * or HTA [2] bodies
- Scientific Advice on PASS [3]
- Not legally binding & fee reduction for SME and Academia & pediatric MPs

- Additional information: Scientific Advice
- scientificadvice@ema.europa.eu

ATMP classification

- Scientific recommendation of the CAT* if ATMP, i.e. for borderline products
- Facilitation of regulatory procedure
- Orientation for national agencies

- Free of charge
- Evaluation process takes max. 60 days
- Not legally binding
- Outcome of assessment published by EMA

- Additional information: Classification
- advancedtherapies@ema.europa.eu

ATMP certification

- Certification of quality and non-clinical data by the CAT
- identify potential issues prior to marketing authorisation application (MAA)

- Only pre-assessment procedure
- Evaluation process takes max. 90 days
- Not (yet) open to «academia»

- Additional information: Certification
- advancedtherapies@ema.europa.eu

PRIME –PRIority MEdicines

To foster the development of ***medicines with major public health interest.***

Reinforce scientific and regulatory advice

- Foster and facilitate early interaction
- Raise awareness of requirements early in development

Optimise development for robust data generation

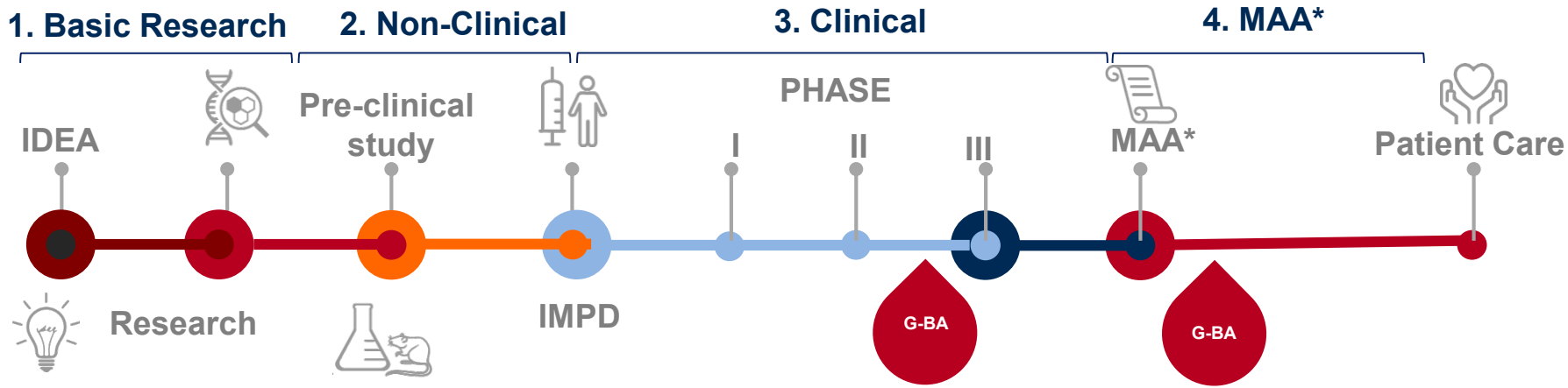
- Focus on efficient development
- Promote generation of robust and high quality data

Enable accelerated assessment

- Promote generation of high quality data
- Facilitated by knowledge gained throughout development

Additional information: PRIME
prime@ema.europa.eu

Overview regulatory support



PEI

Pre-Advice

Scientific Advice

Joint Advice

NCAs

Simultaneous National Scientific Advice (SNSA)

EMA

Scientific Advice, Protocol Assistance

ITF[1] -Meetings

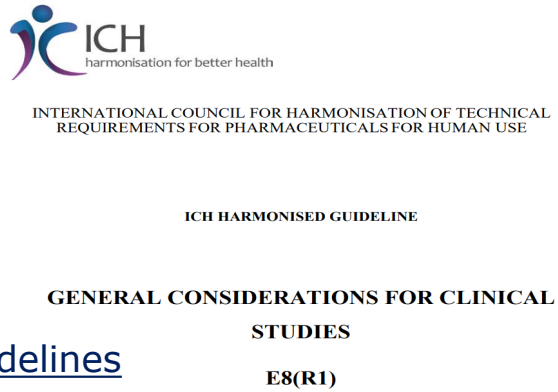
Classification

Certification

*Marketing authorisation application
[1] Innovation task force

Landscape of links to scientific guidance

- Gene therapy medicinal products
- Cell-therapy and tissue engineering
- Quality guidelines
- Quality of medicines: questions & answers
- Biological guidelines
- Non-clinical guidelines
- Clinical efficacy & safety guidelines
- Multidisciplinary guidelines
- International Conference for Harmonisation (ICH) guidelines



Guidelines on ATMP

Quality:

- Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019)

Biologicals: drug substance

- Use of transgenic animals in the manufacture of biological medicinal products for human use (3AB7A)
- Tests on samples of biological origin (3AB11A)

Clinical safety and efficacy

- Existing clinical guidance for the studied indication(s) should be consulted
- Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (EMEA/CHMP/BWP/271475/2006)
- **Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008)**
- **Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)**
- Points to consider on applications with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)

Vaccines

- Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (EMA/CHMP/VWP/141697/2009)

Guidelines on GTMP

Gene therapy

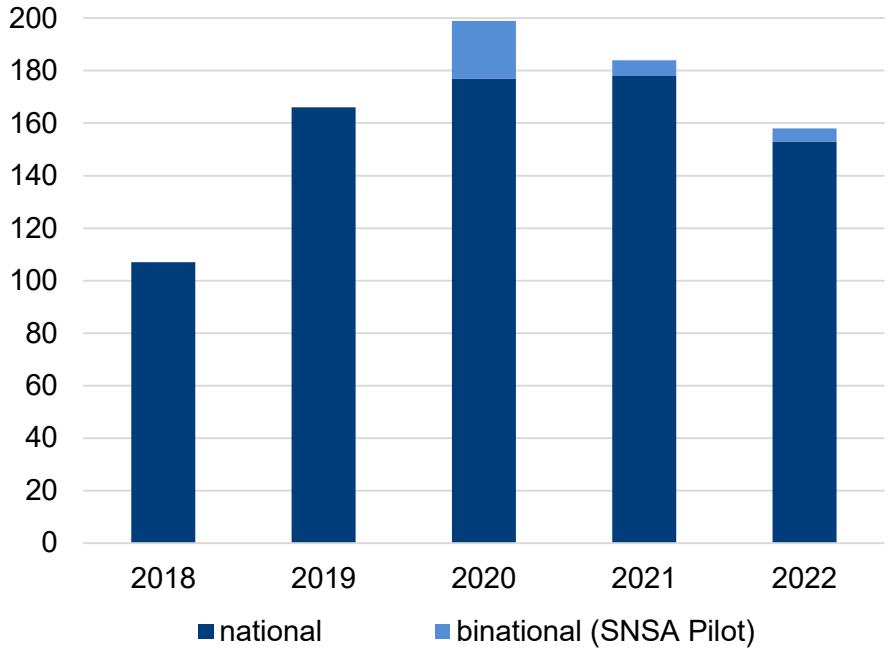
- Questions and answers on gene therapy (EMA/CAT/80183/2014)
- The overarching guideline for human gene therapy medicinal products is the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
- Reflection paper on management of clinical risks deriving from insertional mutagenesis (CAT/190186/2012)
- Reflection paper on design modifications of gene therapy medicinal products during development (EMA/CAT/GTWP/44236/2009)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CAT/CHMP/GTWP/671639/2008)
- Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral vectors (CHMP/GTWP/587488/07)
- Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (CHMP/GTWP/125491/06)
- Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs) (EMEA/CHMP/BWP/473191/2006)
- Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)
- Guideline on non-clinical testing for inadvertent germline transmission of the gene transfer vectors (EMEA/273974/2005)
- Guideline on development and manufacture of lentiviral vectors (CHMP/BWP/2458/03)

Guidelines on SCT & TEP

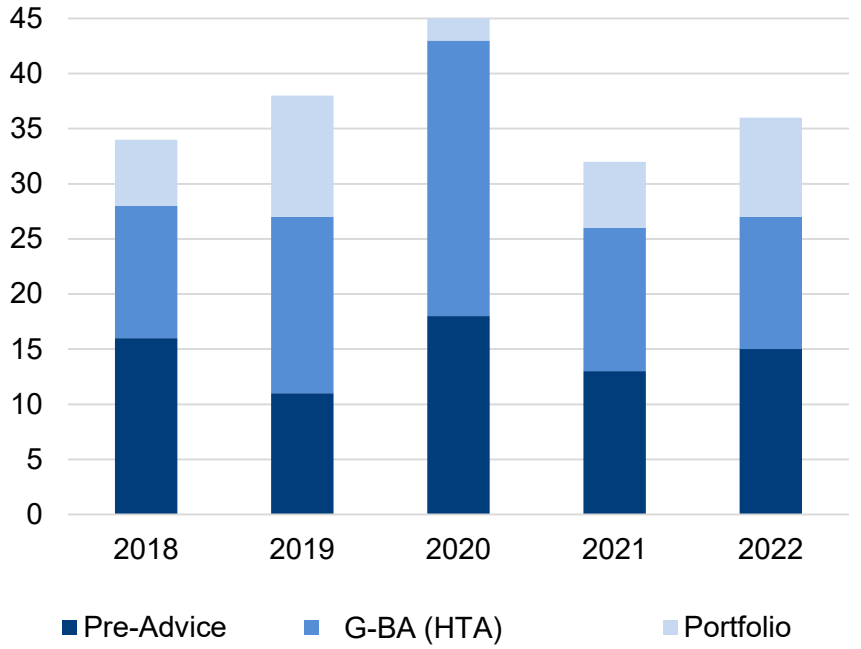
- The overarching guideline for human cell- based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
- Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009)
- Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009)
- Guideline on xenogeneic cell-based medicinal products (EMEA/CHMP/CPWP/83508/2009)
- Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (CHMP/BWP/271475/06)
- Reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009)
- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008)
- Position statement on the use of tumorigenic cells of human origin for the production of biological and biotechnological medicinal products (CPMP/BWP/1143/00)

Data on national Advice

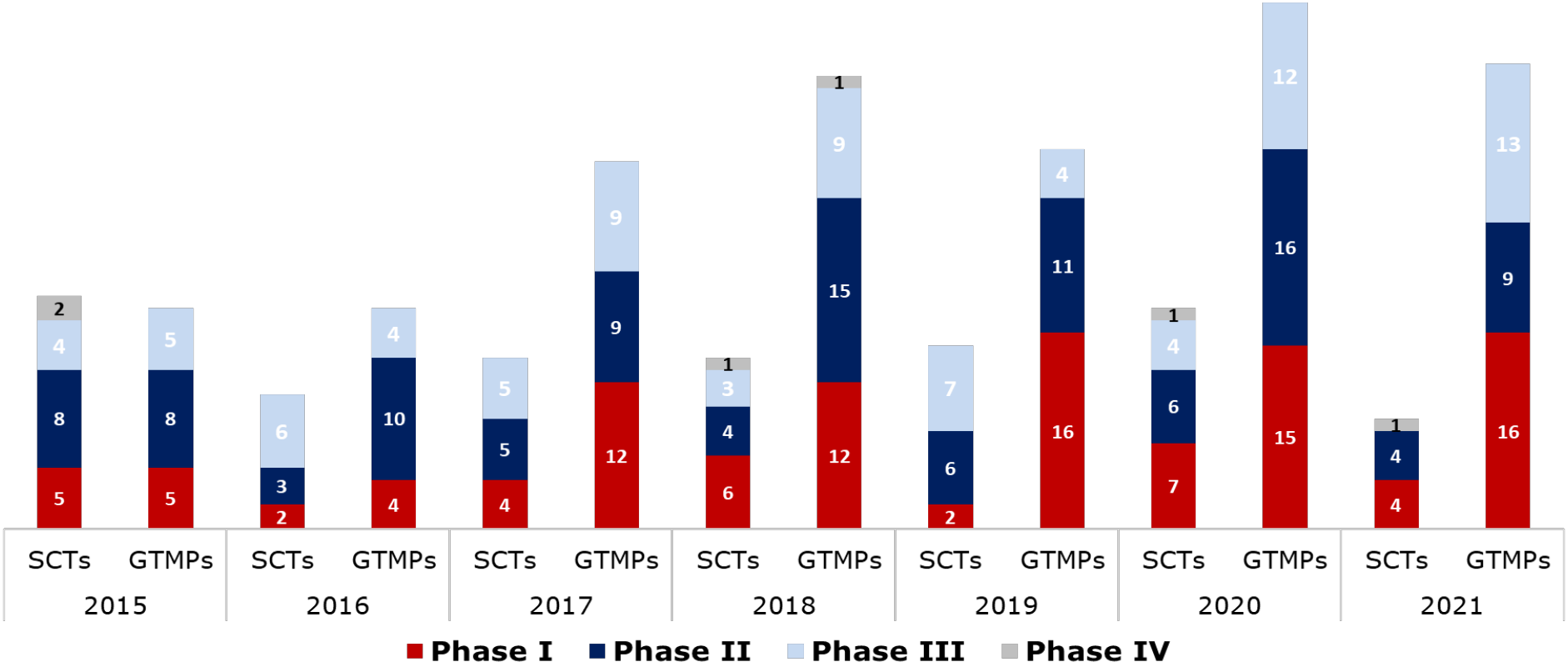
Scientific Advice



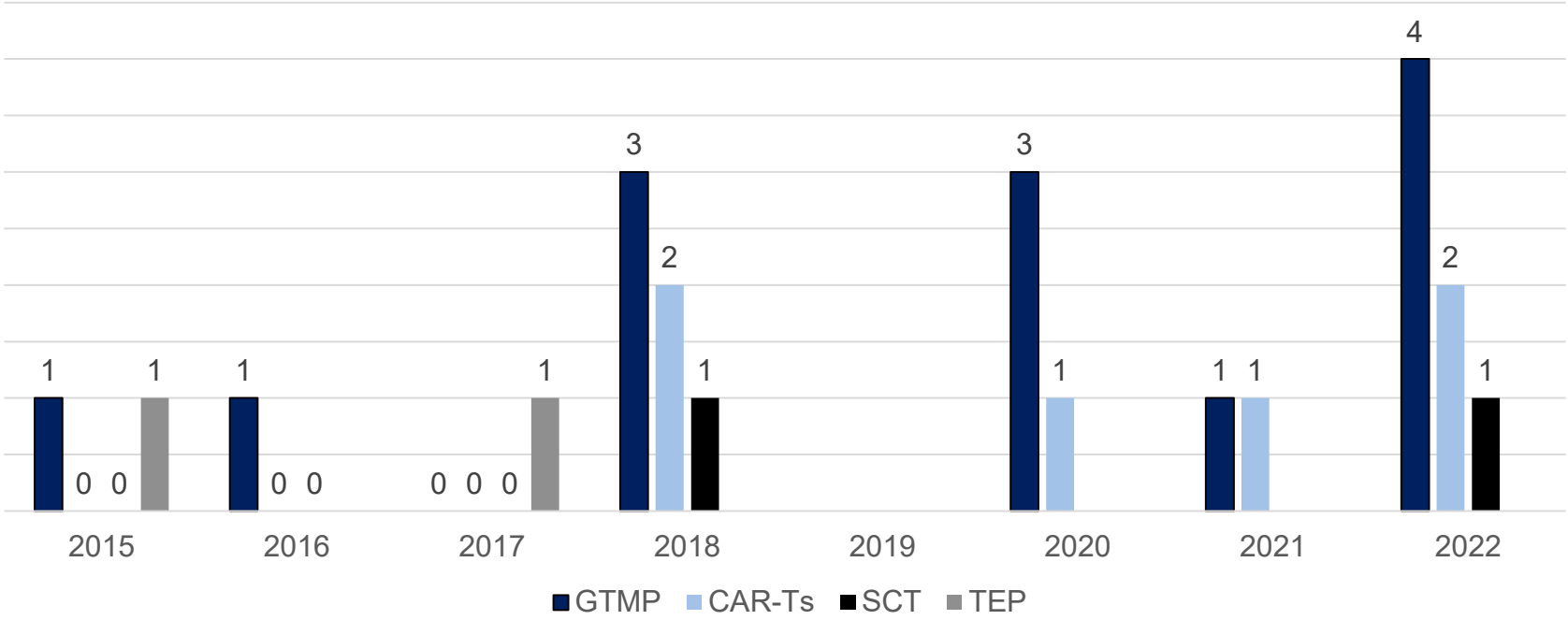
Other advice formats



Clinical trials applications for GTMP & SCT at the PEI

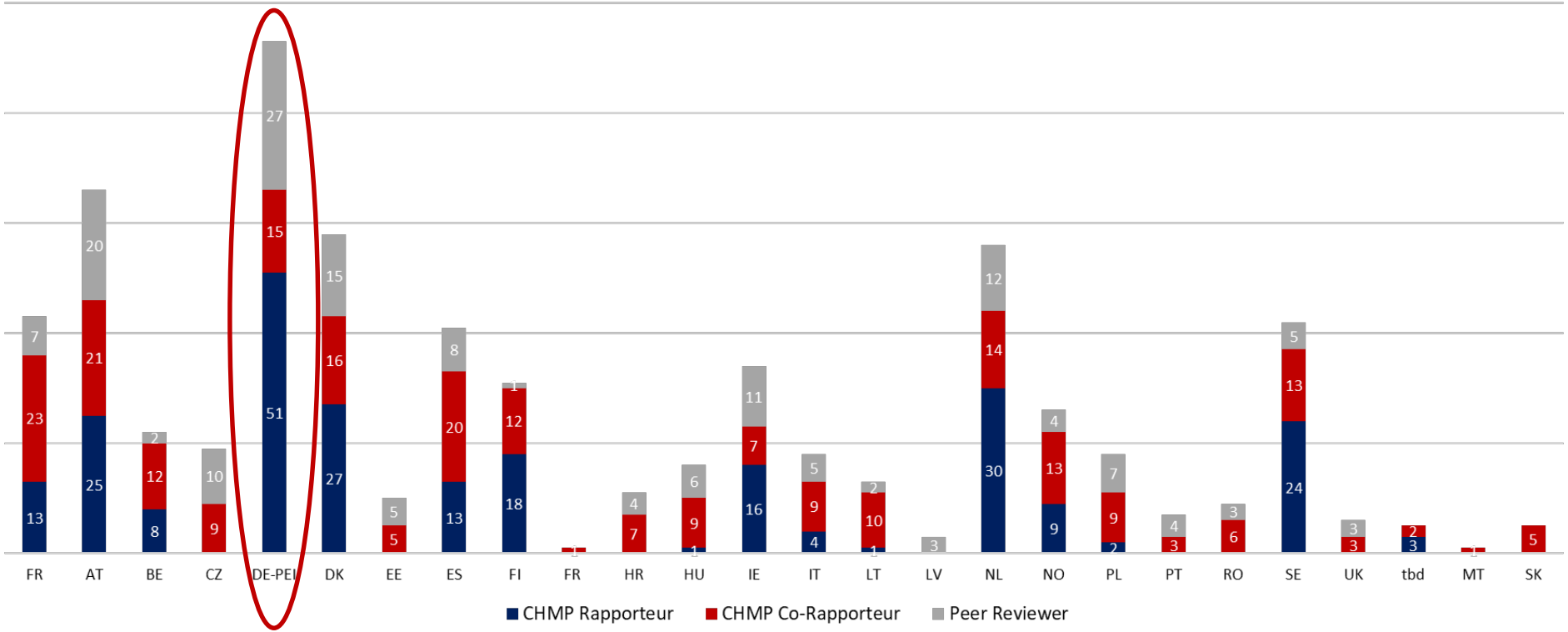


Authorised ATMP in the EU



Orphans: 15

Centralised procedures[1)] - European overview 2017-2022



[1)] Products within PEI remit

Paul-Ehrlich-Institut – our focus is on health

Thank you for your attention

Further information: www.pei.de
Contact: Bettina.Ziegele@pei.de