Bundesamt für Sicherheit im Gesundheitswesen
BASG

Introduction

The ATMP Regulation and the Role of the CAT: Have we delivered?

Ilona Reischl, PhD
BASG/AGES - Federal Office for Safety in Health Care
Austrian Agency for Health and Food Safety
Institute Surveillance
Traisengasse 5, 1200 Vienna, Austria

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Bundesamt für Sicherheit im Gesundheitswesen
BASG

The starting point

Regulation (EC) No 1394/2007

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

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.

Effective since
30 December 2008
‘Lex specialis’

The motivation

Key elements relating to CAT

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- 5) Because of the novelty, complexity and technical specificity of ATMPs, 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.

- 10) The evaluation of ATMPs often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within the Agency, a Committee for Advanced Therapies (CAT), which should be responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by the Agency's CHMP. In addition, the CAT should be consulted for the evaluation of any other medicinal product which requires specific expertise falling within its area of competence

- 11) The CAT should gather the best available expertise on ATMPs in the Community. The composition of the CAT should ensure appropriate coverage of the scientific areas relevant to ATMPs, including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigilance and ethics. Patient associations and clinicians with scientific experience of advanced therapy medicinal products should also be represented.

REG (EC) No 1394/2007 on ATMPs

Article 23 Tasks of the CAT

Bundesamt für Sicherheit im Gesundheitswesen
BASG

a) to formulate a draft opinion on the quality, safety and efficacy of an ATMP for final approval by the CHMP and to advise the latter on any data generated in the development of such a product
b) to provide advice, pursuant to Article 17, on whether a product falls within the definition of an ATMP
c) at the request of the CHMP, to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 21(2);
d) to provide advice on any question related to ATMPs, at the request of the Executive Director of the Agency or the Commission;
e) to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation;
f) at the Commission's request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas referred to in Article 21(2);
g) to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004

REG (EC) No 1394/2007 on ATMPs

Bundesamt für Sicherheit im Gesundheitswesen
BASG

CAT also:

a) participates in certifying quality and non-clinical data for small and medium-sized enterprises developing ATMPs;
b) participates in providing scientific recommendations on the classification of ATMPs;
c) contributes to scientific advice, in cooperation with the Scientific Advice Working Party (SAWP);
d) takes part in any procedure delivering advice on the conduct of efficacy follow-up, pharmacovigilance or risk-management systems for ATMPs;
e) advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety or efficacy;
f) assists scientifically in developing any documents relating to the objectives of the Regulation on ATMPs;
g) provides scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs;
h) supports the work programmes of the CHMP working parties.

The numbers

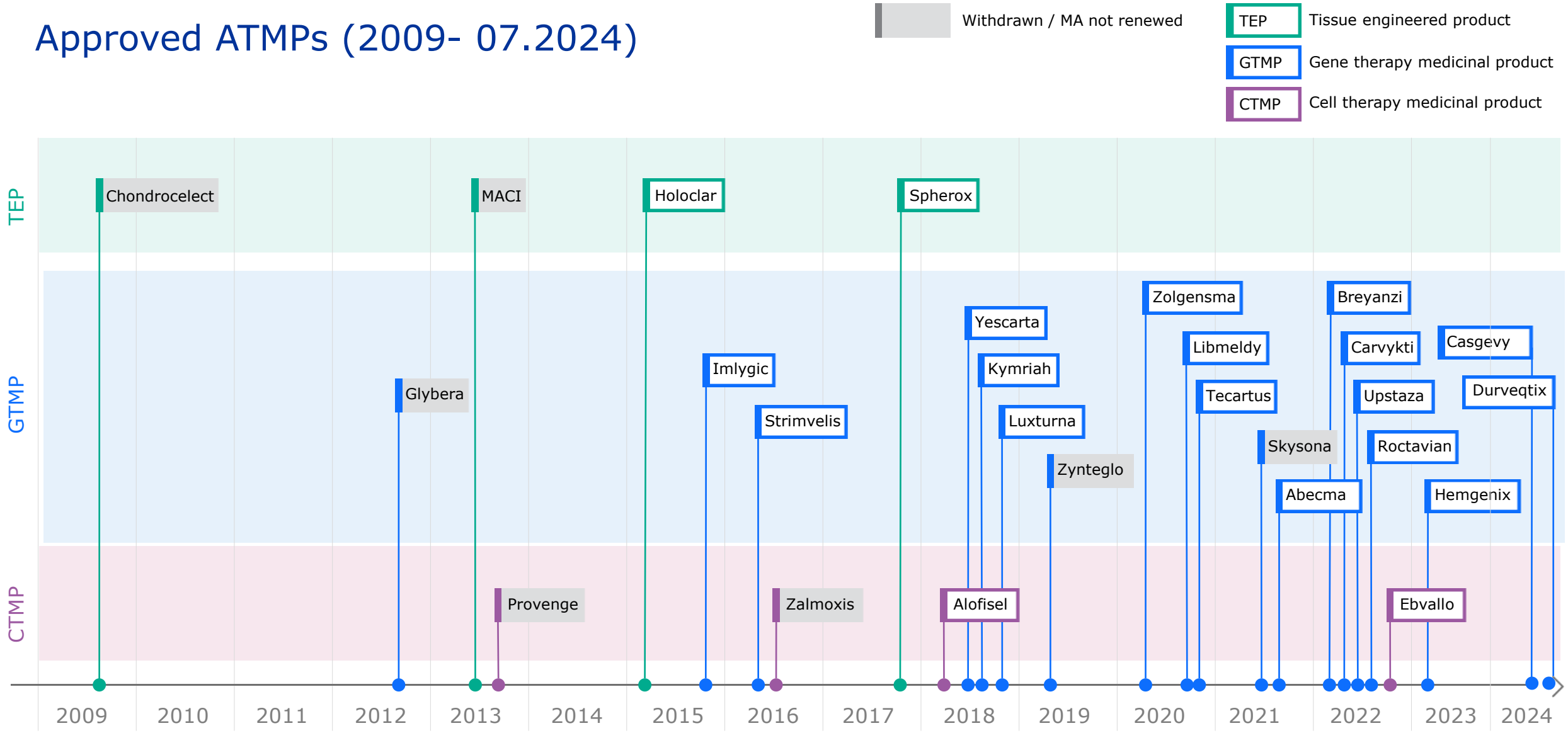
EMA procedures 2009 - July 2024

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Submitted MAAs: 44 → **28** positive, **4** negative draft opinions

  10 withdrawals and **7** procedures ongoing
- Type II variations: **227**
- Classifications: **673** submitted - **665** positions adopted
- Scientific advice: **650**
- PRIME (ATMP): **139** discussed - **65** granted

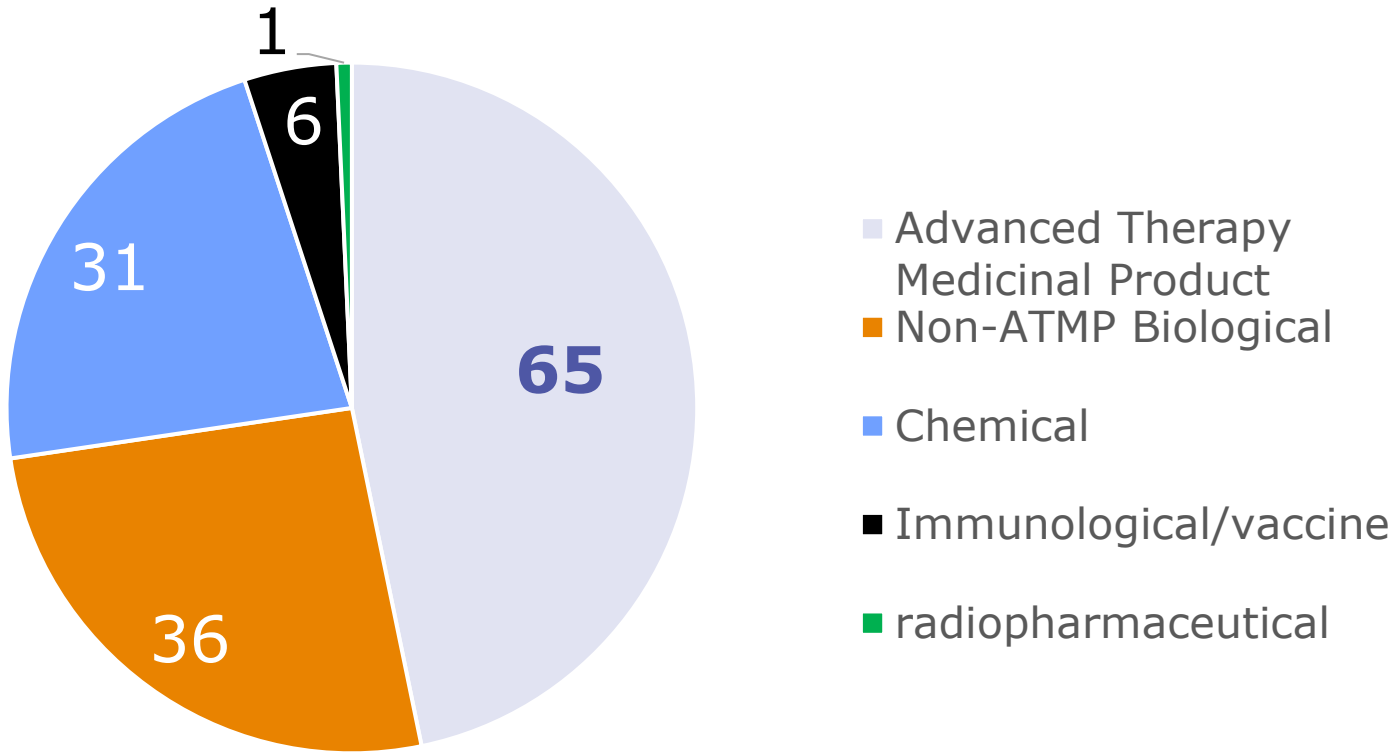
Approved ATMPs (2009- 07.2024)



ATMPs and PRIME procedures

ATMPs 27% of applications, 47% of products granted

ATMP	65
Non-ATMP Biological	36
Chemical	31
Immunological/ vaccine	6
radiopharmaceutical	1
Total	**139**



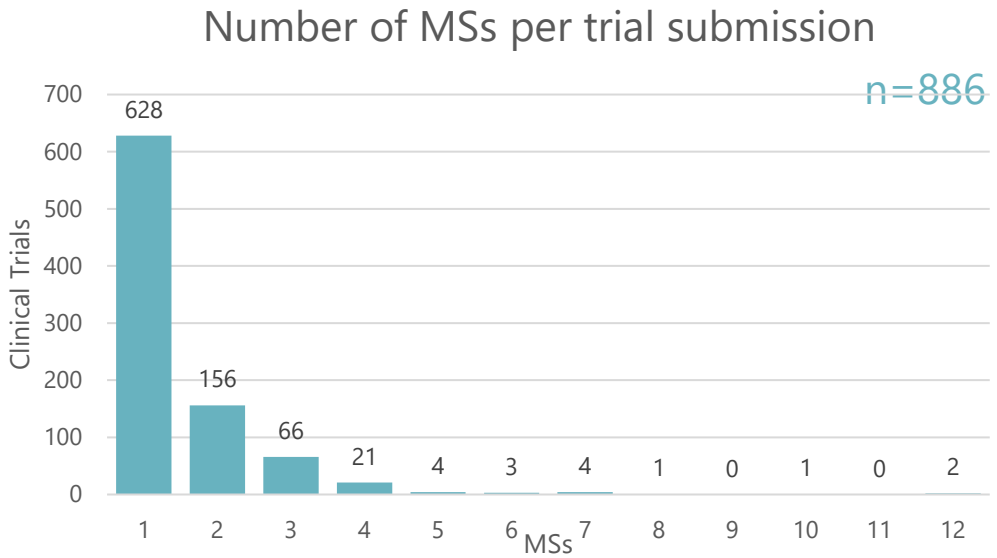
Slide by K. Cunningham EMA

The numbers

Bundesamt für Sicherheit im Gesundheitswesen
BASG

ATMPs in development - Clinical trial submissions in the EU 2016-2023

Updated and clarified



Preliminary curated analysis (EudraCT **and** CTIS) submissions and number of member states concerned
Follow-on from
CTs 2009-2016 - Boran et al. DOI: 10.1089/humc.2016.193

The numbers

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

ATMP guidance documents by CAT and in contribution with other groups

Gene therapies and genetically modified cells

7 Guidelines

3 Reflection Papers

2 Q&A

Cell-based Medicinal Products

1 Guideline

3 Reflection Papers

4 Q&A

4 Additional guidances on classification, GMP, GLP and GCP for ATMPs

Workshops and meetings

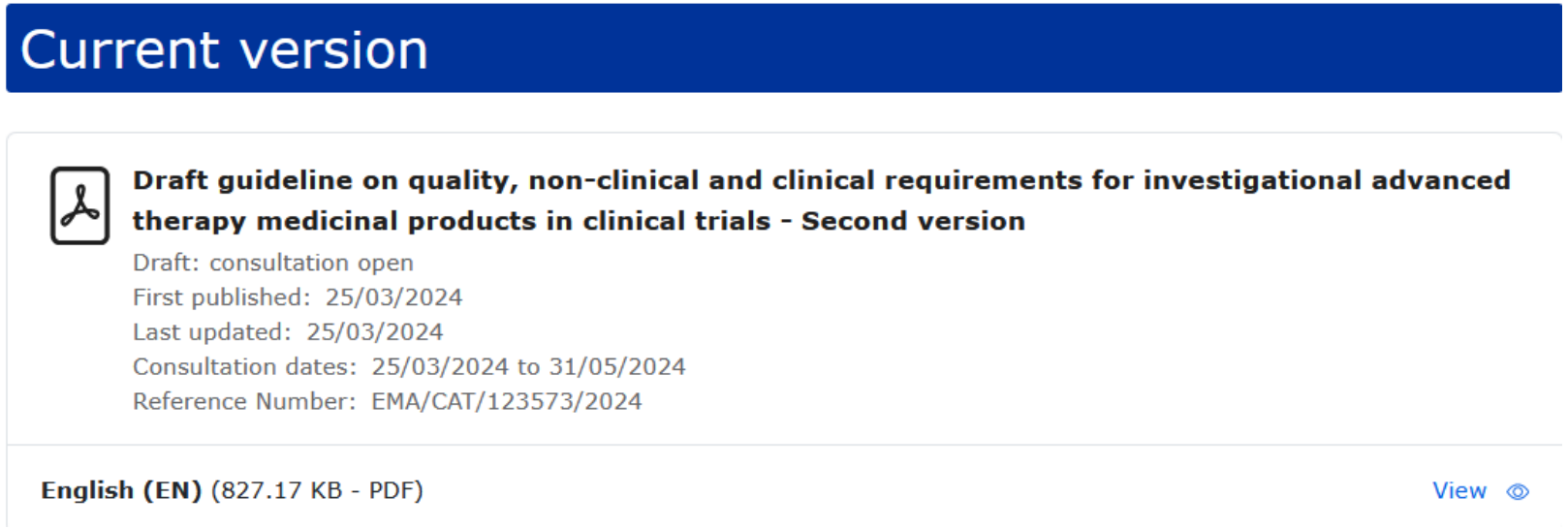
Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

- First EMA Workshop on ATMPs (2/4/2009)
- Since then, CAT as a committee and its members as individual speakers have participated in numerous workshops and conferences to transmit regulatory knowledge to stakeholders and understand the challenges for developers
- CAT members have contributed and are contributing to international initiatives
- CAT members in their National roles are contributing to ATMP related training and serving as experts for ATMP related issues

Current guideline activities

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Guideline on Q, NC and C requirements for investigational ATMPs in clinical trials – with CTCG



Started in 2015, delayed due to Brexit and Pandemic, revised, 2nd consultation

Comments addressed, planned finalisation of GL by end of Q4 2024

www.ema.europa.eu/en/guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy-medicinal-products-clinical-trials-scientific-guideline

The multiplication factor

CAT and CAT members are active in

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- National support:
  - answering specific questions, providing guidance on websites and in meetings
  - National scientific advice
- EU and internationally
  - EMA procedures
  - By contributing to the European network – EMA and non-EMA working groups
  - Guidance development, training activities (ATMP curriculum)
  - By raising regulatory issues to legislators
  - By contributing to International activities – WHO, ICH, ….

- *Of note* – other than the formal procedures, none of these activities generate income for National Agencies and are usually done on top of routine work

Challenges for National Competent Authorities

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Resources

- Adherence to planned submission dates is vital for planning of assessor resources
- Complexity of procedures comparatively binding more resources (first-in-class, interfaces, …)
- Overall number of ATMP assessors for authorization procedures per agency – competition for the same assessor pool between biologic and ATMP procedures
- Frequency of linked non-paid activities related to the ATMP topic
- Additional resources needed for international harmonization activities
- Experienced ATMP assessors are in high external demand → succession planning

Lessons learned in fostering ATMP development

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Need for an interlinked perspective

- ATMPs are medicinal products and their quality, safety and efficacy needs to be demonstrated on a product-specific basis! → medicinal product framework
- The field can only mature when robust and reproducible data are generated, e.g. good science, good documentation, sufficient follow up → clinical trial framework
- Clinical trial procedures and interface aspects need to be clear → legal and procedural framework, classification support
- Exemptions for individual needs, when implemented, need to be clearly defined → policy
- Need for close interaction with patients → inclusion on all levels
- Need for a clear policy on what is acceptable and what not → enforcement
- Patient access needs to be facilitated, implementation of HTA regulation → organisational setup of the health system
- Good science and regulatory compliance has it's cost → funding

So, are we all done?

My personal opinion

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- The ATMP Regulation references the novelty, complexity and technical specificity of ATMPs
- Nowadays it is often stated that ATMPs are mainstream and no different than many other medicinal products – usually by the same speakers that emphazise the novelty, complexity and special need for support for ATMPs
- Technological advance has made ATMP manufacture more accessible
- We still have scientific questions
- Innovation is rapid and brings new questions and complexities, e.g. genome editing, device components, companion diagnostics
- New areas of intensified need for input arise → Health Technology Assessment interface
- The CAT is serving as the forum to bring these issues forward for expert discussion

Conclusion

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- The CAT has fulfilled the tasks dictated by the ATMP Regulation
- It has facilitated the coming together of European ATMP experts
- It has served as a platform and source of knowledge for European experts
- It has served the field
- It has served as a contact point for ATMP developers
- Future structures need to serve these needs and the momentum needs to be maintained!

Thank you!

To our three former chairs

To our dedicated EMA support team

To our engaged CAT members
specifically the patients' and physicians' representatives

To all contributing colleagues from the EU network