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Advanced-therapy medicinal products: new competencies in hospital pharmacy
Seminar PH4

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Disclosure

Relevant Financial Relationships - None

Off Label Investigational Uses - None

Learning objectives

- Overview of legal framework pertaining to ATMPs
- Classification of ATMPs
- Definitions and types of ATMPs
- Examples for (marketed) ATMPs

Questions

1) Can an ATMP be marketed in one EU member state only?

2) Can a general manufacturing authorisation for ATMPs be obtained?

3) Can a chemical compound be classified as ATMP?

Overview legal framework

What to look for	Where to find it
! Overall framework	Regulation (EC) No 1394/2007
! ATMP classification	Directive 2001/83/EC Commission Directive 2009/120/EC
! SME data certification	Commission Regulation (EC) No 668/2009
! Scientific and technical requirements	Commission Directive 2009/120/EC
[Conditional] MA and supervision	Regulation (EC) No 726/2004 [Commission Regulation (EC) No 507/2006]
Clinical trials	EU Directive 2001/20/EC, to be repealed by EU Clinical Trial Regulation No 536/2014 Commission Directive 2005/28/EC (GCP) Commission Directive 2003/94/EC (GMP)
Paediatric regulations	Regulation (EC) No 1901/2006 Regulation (EC) No 1902/2006

Overview legal framework ctd.

What to look for	Where to find it
Variations regulation (regarding MA)	Commission Regulation (EC) No 1234/2008
Pharmacovigilance	Regulation (EU) No 1235/2010 Regulation (EU) No 1027/2012 Directive 2010/84/EU Directive 2012/26/EU Commission Implementing Regulation No 520/2012
Personal data protection	Directive 95/46/EC
! Tissue, cells and traceability	Directive 2004/23/EC Directive 2006/17/EC Directive 2006/86/EC Directive 2015/565 Directive 2015/566
! Human blood and blood components	Directive 2002/98/EC
! GMOs	Directive 2001/18/EC

A little digression on ‚Legalese'

- A "regulation" is a binding legislative act. It must be applied in its entirety across the EU. A regulation is similar to a national law with the difference that it is directly applicable in all EU countries.
- A "directive" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals. Directives are therefore to be transferred into national law by each country as they deem appropriate.

Types of ATMPs

1) tissue-engineered products

   → defined in Regulation (EC) No 1394/2007

2) gene-therapy medicinal product
3) somatic cell-therapy medicinal product

   → defined in Part IV of Annex I to Directive 2001/83/EC

Commission Directive 2009/120/EC (amending Directive 2001/83/EC) provides further scientific and technical requirements for all types of ATMPs

tissue-engineered products (TEP) - definition

- TEPs contain cells or tissues to regenerate, repair or replace human tissue
- May contain living or dead cells/tissues from human or animal origin with or without further substances. Dead cells/tissues without pharmocological, immunological or metabolic effect are not regarded as TEPs
- Contained cells/tissues do not fulfill the same function in the host as in the donor (non-homologous use).

tissue-engineered products on the market

Currently 2 products on the market in Europe (one withdrawn, 5 products in Germany):

- characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins, for the repair of damaged cartilage
- patient's own limbal cells, which include cells from the surface of the cornea and limbal stem cells grown in a laboratory, to treat moderate to severe limbal stem-cell deficiency caused by burns, including chemical burns, to the eyes (orphan disease)

gene-therapy medicinal product - definition

- an active substance consisting of or containing a recombinant nucleic acid, aiming to add, regulate, repair, substitute or delete a genetic sequence
- The therapeutic, prophylactic or diagnostic effect is directly due to this recombinant nucleic acid
- *Exemption*: *drugs, which fulfill both criteria above, but are intended to be used as vaccines against infectious diseases, are not considered a gene-therapy medicinal product*
- Environmental Risk Assessment (ERA) necessary for deliberate release approval: assessment of the potential harmful effects (direct/indirect, immediate/ delayed) of a GMO for humans, animals, plants, microorganisms and the environment at large

gene-therapy medicinal product on the market

- One product available in Europe so far: a virus-derived gene vector for the treatment of Lipoprotein Lipase (LPL) deficiency, having caused pancreatitis, manufactured in insect cells

somatic cell-therapy medicinal product - definition

- Contains cells or tissues with a pharmocological, immunological or metabolic effect which is used to treat, prevent or diagnose a disease
- Its biological characteristics, physiological function or structural properties were substantially altered for ist clinical use
- Contained cells/tissues do not fulfill the same essential function in the host as in the donor (non-homologous use).

somatic cell-therapy medicinal products on the market

- Currently none on the market in Europe, 2 authorised in Germany (tumor vaccines)
- One authorised in 2013, an autologous, dendritic cell product used as tumor vaccine in prostate cancer, but withdrawn in 2015 for unknown reasons

ATMP classification and authorisation

- Manufacturers may consult EMA (in Germany also national authority “PEI”) to verify whether their medicinal product meets the scientific criteria for defining an ATMP
- ‘Innovation Task Force’ in place for scientific advice
- classification procedure is optional
- Scientific recommendations are given by EMA's Committee for Advanced Therapies (CAT), summaries are published on EMA homepage
- micro-, small- and medium-sized-enterprise (SME) office in place
- Marketing authorisation must be obtained centrally via EMA (marketing authorisation number starts with “EU/… “
  - Of course there are exemptions from this rule, at least in Germany (“PEI.A. ….)

Exemption from central authorisation

According to § 4b of the German Medicines Act (AMG), ATMPs may be exempt from central authorisation, if:

1.It is prescribed by a physician as an individual preparation for a single patient

2.Is not routinely manufactured according to specific quality standards

- ie in small quantity and with deviations in routine manufacturing due to medical reasons
- Or if not yet manufactured in sufficient quantities to reach final conclusion on the product

3.And is administered in a specialised health care institution under supervision of a physician

Authorisation by national competent authority (PEI), offers consultation on questions regarding authorisation procedures

Excerpt from the public consultation on the Delegated Act dreg_on_gmp_for_imp_2015_rev_180815

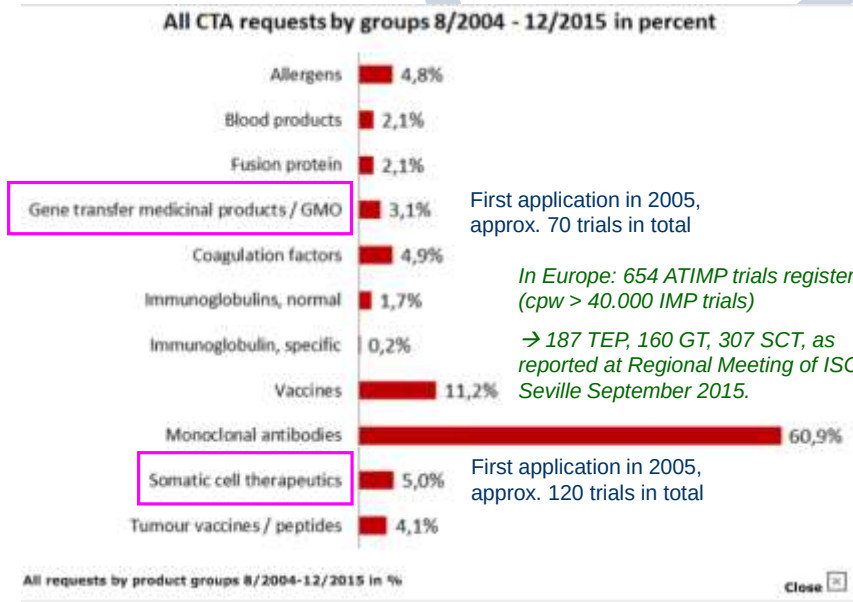
Excerpt from

The public consultation (August 2015) document on the:

'Commission Delegated Act on Principles and guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedures, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014'

"The requirements of Good Manufacturing Practices shall be adapted to the specific characteristics of ATMPs in accordance with a risk based approach."

German statistics - from www.pei.de/ct-numbers



First application in 2005, approx. 70 trials in total

In Europe: 654 ATIMP trials registered (cpw > 40.000 IMP trials)

→ 187 TEP, 160 GT, 307 SCT, as reported at Regional Meeting of ISCT, Seville September 2015.

First application in 2005, approx. 120 trials in total

Clinical trials

- EU Directive 2001/20/EC – the “clinical trials directive”
  - Art. 13(1): “Member States shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation.”

  → Repealed by EU Clinical Trial Regulation Nr. 536/2014 (current prediction: October 2018)

  → Chapter IX, Art. 61 subjects member states to issuing MAs

Exemption from manufacturing authorisation

- Commission Directive 2005/28/EC – the “GCP directive”
  - → Art. 9(2): “Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for **reconstitution prior to use** or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions.”
- *New EU CT Regulation No. 536/2014 keeps this exemption (Chapter IX, Art. 61 (5))*

Definition reconstitution

EudraLex Vol. 4 – EU-GMP Guidelines
→Annex 13: Medicinal Products for Human and Veterinary Use

- „…reconstitution shall be understood as simple process of:
  - Dissolving or dispersing the IMP for administration of the product to a trial subject
  - Or, diluting or mixing the IMP(s) with some other substance(s) used as a vehicle for the purposes of administering it
- Reconstitution is **not** mixing several ingredients, including the active substance, together to produce the IMP
- An IMP must exist before a process can be defined as reconstitution
- The process of reconstitution has to be undertaken as soon as practicable before administration
- This process has to be defined in the clinical trial application / IMP dossier and clinical trial protocol, or related document, available at the site

→ Same definition is found in the draft for the ‚Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014'

‚Survey' on ATMPs in European Hospital Pharmacies

- I am facing the same problem right now, as I was asked to reconstitute an investigational gene therapy product for a clinical trial in thalassemia. I am collecting information, but my belief is that, since it is a simple reconstitution (and not a production), in my country (Italy) hospital pharmacies do not require any particular licence or authorization.
- Ireland is guided by the European definition of ATMPs. The regulatory authority in Ireland is the HPRA (Health Products Regulatory Authority). Such therapies are only in their infancy in this country and I am not aware of any hospital pharmacist with experience who could address your questions.
- In Denmark all preparations and reconstitutions have to be released by a QP or delegated QP. This would be the same for ATMPs. None of my colleagues are aware that hospital pharmacies in DK are involved in clinical trials with ATMPs.

Conclusions

- ATMPs are a relatively new and interesting development
- The diversity of the product class ‚ATMP' makes it difficult to regulate
- Health authorities have great interest in advancing ATMP development

Questions

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2) Can a general manufacturing authorisation for ATMPs be obtained?

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References and further reading

- EMA homepage: www.ema.europa.eu → 'human regulatory' → 'adanced therapies'
- Regulation (EC) No 1394/2007
- Directive 2001/83/EC (esp. part IV of annex I)
- Commission Directive 2009/120/EC (amending Directive 2001/83/EC)
- Detailed draft guidelines on GCP specific to ATMPs (EMA)
- EudraLex Vol. 4, EU-GMP, especially Annex 2
- Adopted reflection paper on classification of ATMPs Rev.1 (EMA)
- EMA summary reports of scientific recommendations on classification of ATMPs (homepage)