Advanced therapy medicinal products

- Products and classification
- New procedures and guidelines
- Product-specific considerations

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Bonn, 17 June 2008

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

(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).

Marketing authorisation of advanced therapy medicinal product in all EU members states by a single application for the centralized procedure carried out by EMEA. Review and assessment of the MA dossier by EU MS experts, e.g., from the Paul-Ehrlich-Institut.

A product containing a viable cells is always a medicinal product, not a medical device

(Regulation (EC) No. 1394/2007)

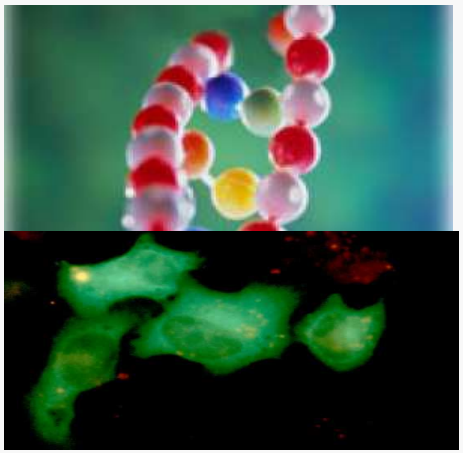
2. Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.

Gene therapy > cell therapy > tissues engineered MPs

advanced therapy products

gene therapy products

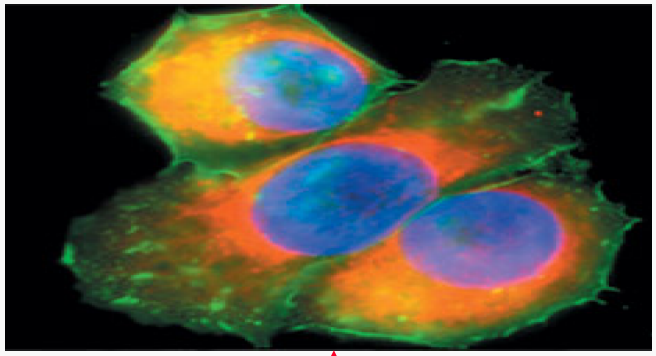
- cells and nucleic acids excluding live virus vaccines,
- including live vector and DNA vaccines



- recombinant nucleic acids in
  - viral or non-viral repl.-incomp. vectors,
  - DNA or RNA,
  - cells,
  - rec. replicating viruses/micro-org.

somatic cell therapy products

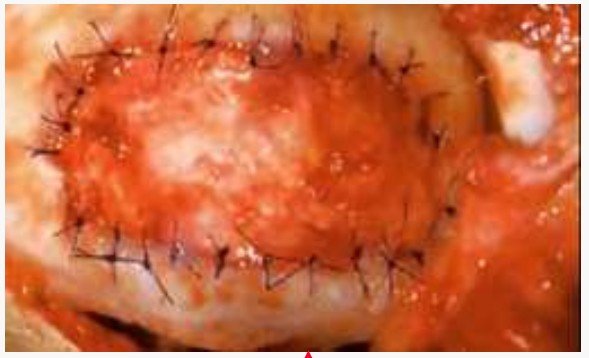
immunological SCTs
- DCs, CTLs, NK cells



- engineered cells used for
  - adoptive immunotherapy,
  - therapeutic vaccination,
  - secreting molecules

tissue engineered products

- ACT, stem cells for tissue repair



- engineered cells used for tissue
  - regeneration,
  - repair or
  - replacement

cell-based products

Definition of Tissue Engineered Product in Regulation (EC) No. 1394/2007

(b) 'Tissue engineered product' means a product that:

— 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.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

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, shall be excluded from this definition.

ANNEX I to Regulation (EC) No. 1394/2007

Manipulations not considered to result in „engineered“ cells

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:

(c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

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

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

— cutting,

— grinding,

— shaping,

— centrifugation,

— soaking in antibiotic or antimicrobial solutions,

— sterilization,

— irradiation,

— cell separation, concentration or purification,

— filtering,

— lyophilization,

— freezing,

— cryopreservation,

classical tissue preparations (national MA)

a few newer TEPs for cardio-vascular disease applications, but non-homologous use (centralized MA via EMEA)

Definition of Combined Advanced Therapy Medicinal Product

(d) 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions:

— it must incorporate, as an 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.

Definition of an ATMP for non-homologous use in Regulation (EC) No. 1394/2007

Final evaluation of combined ATMPs by EMEA and conformity with requirements for medical devices

(Regulation (EC) No. 1394/2007)

Article 9

Combined advanced therapy medicinal products

1. Where a combined advanced therapy medicinal product is concerned, the whole product shall be subject to final evaluation by the Agency.

2. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include evidence of conformity with the essential requirements referred to in Article 6.

3. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include, where available, the results of the assessment by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part.

Article 7

Specific requirements for advanced therapy medicinal products containing devices

In addition to the requirements laid down in Article 6(1) of Regulation (EC) No 726/2004, applications for the authorisation of an advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices shall include a description of the physical characteristics and performance of the product and a description of the product design methods, in accordance with Annex I to Directive 2001/83/EC.

Article 6

Issues specific to medical devices

1. A medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex I to Directive 93/42/EEC.

2. An active implantable medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex 1 to Directive 90/385/EEC.

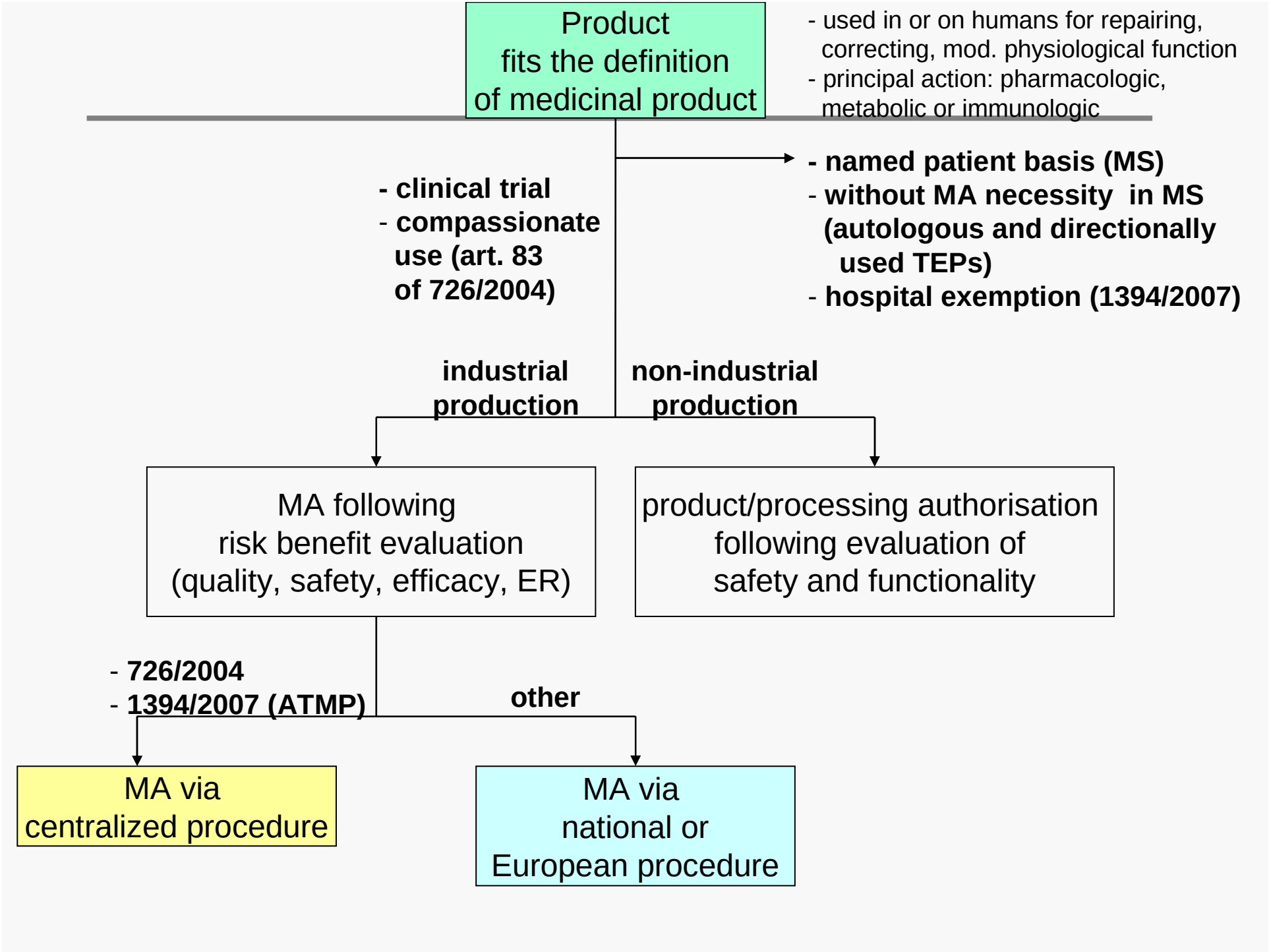
Opinions by stakeholders on the GTMP definition

- Products to be included
  - plasmid DNA (biologically produced nucleic acid)
  - non-viral vector
  - viral vector
  - recombinant and armed oncolytic virus
  - recombinant nucleic acid
  - genetically modified cell
    (cell containing recombinant nucleic acid)

  - nucleic acid-containing products used with a view to regulating, repairing or replacing a targeted genetic sequence
  - genetically modified cells where the recombinant nucleic acid is an added, mutated or deleted genetic sequence

  - products whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid
    or to cells harbouring a nucleic acid which has these properties

- Products under discussion for inclusion:
  - prophylactic vaccines against infectious agents,
  - because there are established requirements.


Product
fits the definition
of medicinal product
- used in or on humans for repairing, correcting, mod. physiological function
- principal action: pharmacologic, metabolic or immunologic
- named patient basis (MS)
- without MA necessity in MS (autologous and directionally used TEPs)
- hospital exemption (1394/2007)
- clinical trial
- compassionate use (art. 83 of 726/2004)
industrial production
non-industrial production
MA following risk benefit evaluation (quality, safety, efficacy, ER)
product/processing authorisation following evaluation of safety and functionality
- 726/2004
- 1394/2007 (ATMP)
other
MA via centralized procedure
MA via national or European procedure

Advanced therapy medicinal products

- Products and classification
- New procedures and guidelines
- Product-specific considerations

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Consequences of classification of a medicinal product as an ATMP

- Classification by EMEA of an MP as ATMP or not (non-binding)
- Marketing authorisation (MA) by the centralized procedure co-ordinated by EMEA

- For SMEs, fee reductions for EMEA procedures of
  - scientific advice and
  - marketing authorisation application (MAA)
- Certification procedure for quality and non-clinical data prior to MAA

- Overarching Guidelines by European Commission (EC) on GCP, GMP and clinical follow-up of patients:
  - tracking of donated tissues and cells,
  - specific requirements for ATMPs,
  - follow-up for safety and efficacy.
- Opinion drafted by CAT and requirements of Part IV, Annex I to Directive 2001/83/EC apply.

Transitional periods
for some Advanced Therapy Medicinal Product

(Regulation (EC) No. 1394/2007)

Article 29

Transitional period

1. Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

2. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.

In some EU member states, autologous and directionally used TEPs are currently on the market on the basis of a governmental manufacturing authorisation only.

Certification of quality and non-clinical data obtained for Advanced Therapy Medicinal Products

(Regulation (EC) No. 1394/2007)

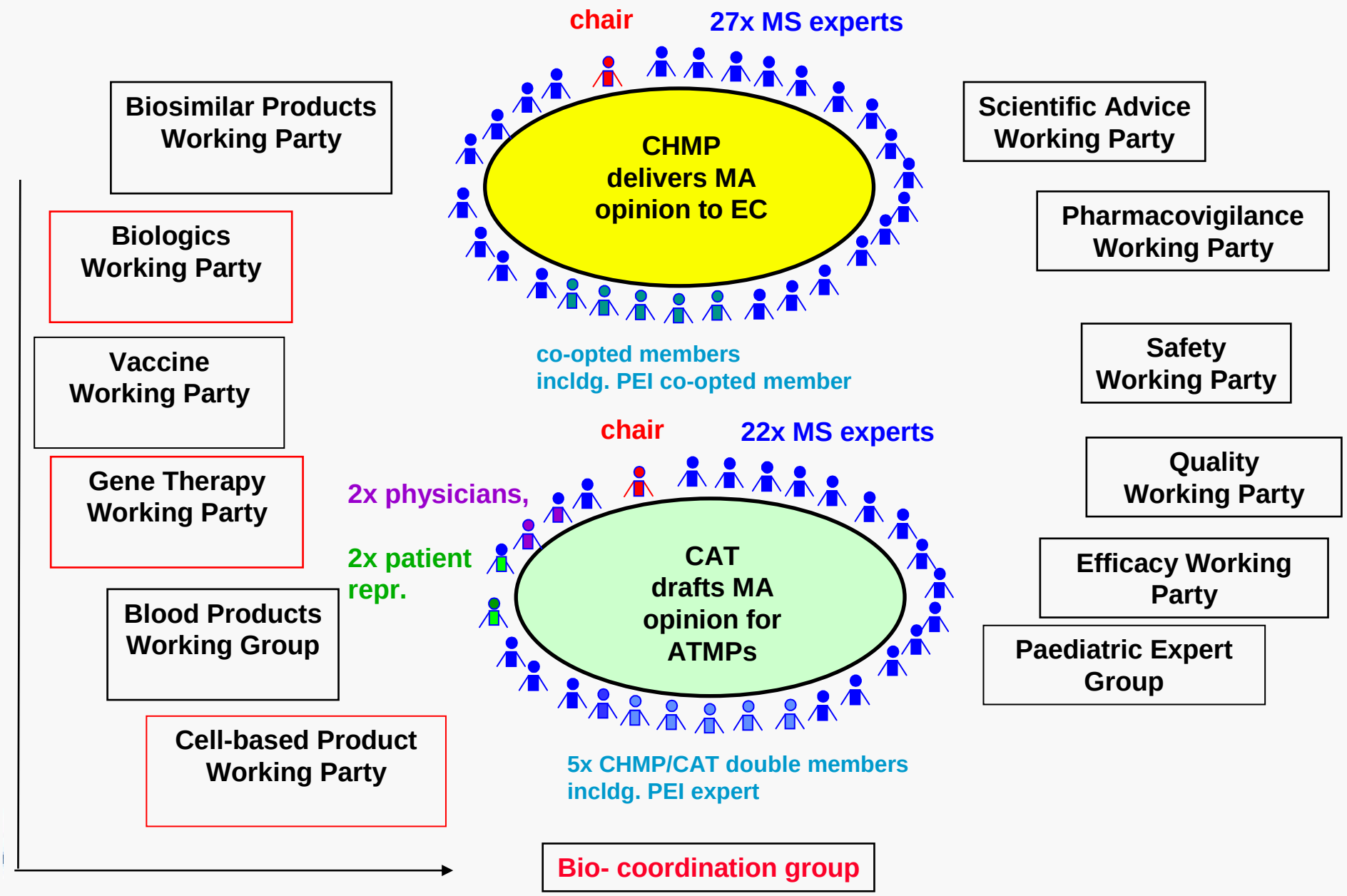
Article 18

Certification of quality and non-clinical data

Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

The Commission shall lay down provisions for the evaluation and certification of such data, in accordance with the regulatory procedure referred to in Article 26(2).

EMEA/CHMP, CAT and Working Parties: Medicines Agencies in EU MS and EMEA in a network



Advanced therapy medicinal products

- Products and classification
- New procedures and guidelines
- Product-specific considerations

Calculated risk: the use of viral vectors to deliver corrective genes to a patient can cause side effects.

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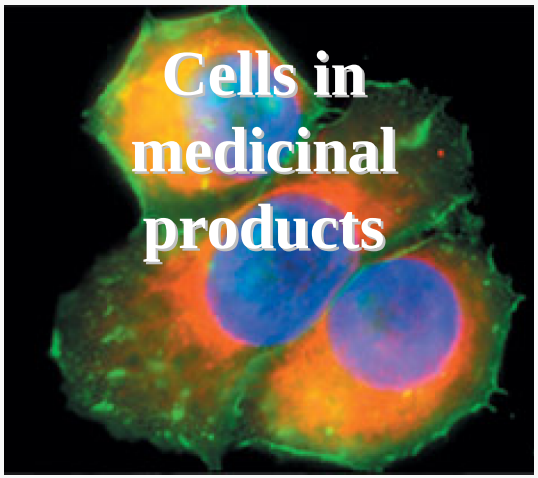
Bonn, 17 June 2008

A human somatic cell as the active (drug) substance in a medicinal product

Cell behaviour in vivo
- migration
- attraction or repulsion of other cells
- differentiation
- half life in vivo
- natural function in vivo (structure, immunological, etc.)

Intracellular molecules
- transcriptome (mRNAs, siRNAs/shRNAs, etc.
- translated peptides, proteins
- fatty acids
- activity of proto-oncogenes and tumour suppressor genes

Release of factors
- growth factors
- cytokines
- chemokines
- functional peptides



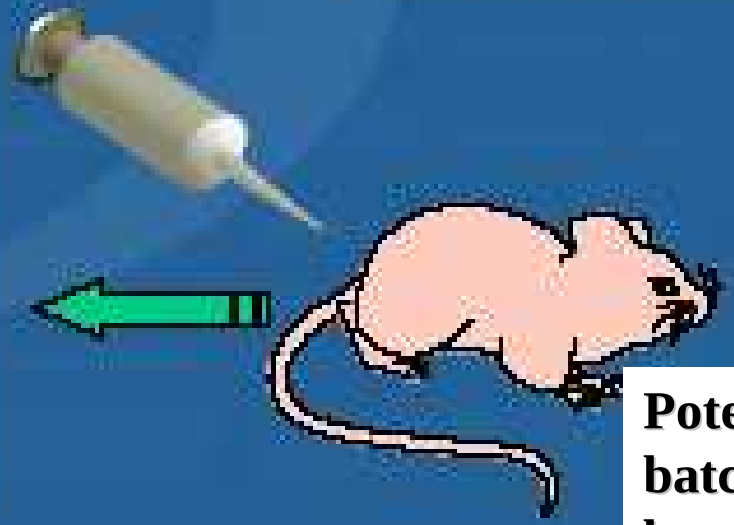
Intracellular state
- signal transduction pathways
- calcium release
- metabolic functions
- stored active peptides and proteins

Genomic state
- cytogenetic abnormalities
- telomers
- activation of proto-oncogenes
- activity

Expression of cell surface molecules related to function and phenotype
- CDs
- growth factor receptores
- cytokine receptors
- chemolkine receptors
- TCRs

Hyalo-cartilage formation in immuno-suppressed nude mice as a potency assay for chondrocyte progenitor cells

Potency prior to first clinical use: first evidence for potential clinical mechanism of action and efficacy



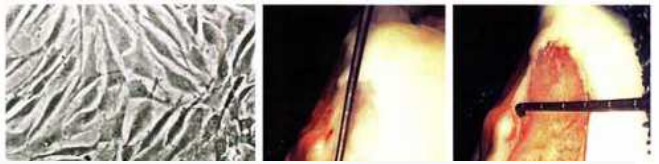
Potency assay for batch release: based on genomics

Dell'Accio et al, Arthritis Rheum, 2001

Human Tissue Engineered Products: examples

Cartilage repair

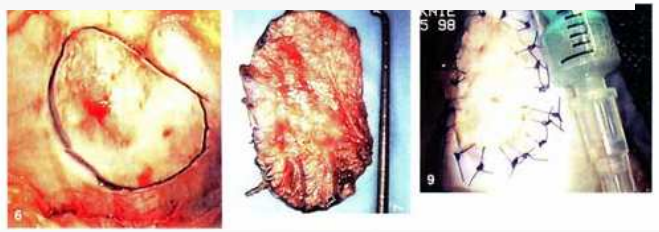
- Autologous chondrocyte transplantation (ACT)
  1st and 2nd generation products



-> only non-inferiority to conv. method demonstrated after 1 year

Skin regeneration

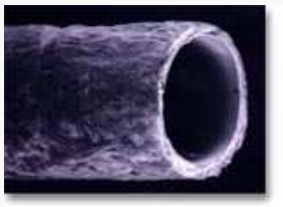
- Acute wounds, diabetic foot skin ulcers
- different skin cells (keratinocytes, fibroblasts)
  in combination with a sheet-like matrices/scaffol



-> ulcer healing may not be predicitive for risk of amputation

Bone regeneration

- Osteoblasts or bone-marrow-derived stem cells
  with ceramic-based scaffolds or biomaterials



Cardiovascular regeneration

- Hematopoetic stem cells for heart muscle
  regeneration

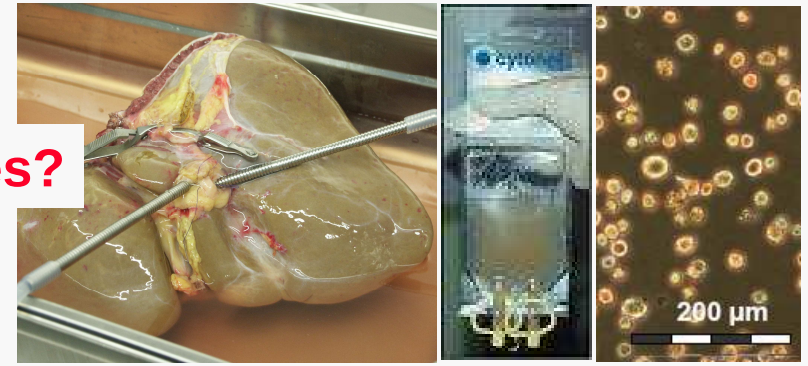
-> mechanisms underlying cell administration: cells or cytokines?

Cell Therapy Medicinal Products: examples

Liver repair

- Allogenic liver cell suspension for treatment of acute sepsis

-> reduction of number of fatal outcomes?

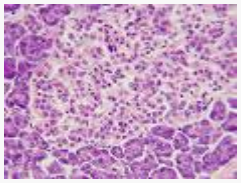


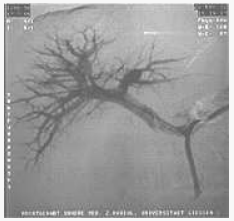
Type I Diabetes

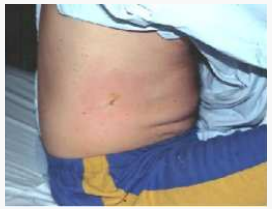
- Allogenic pancreatic islet cell fractions to restore insulin production

Skin repair

- Various skin cell suspensions for treatment of acute wounds and diabetic foot skin ulcers
- Autologous adipose-derived stem cells for treatment of anal fistula







Immunotherapeutics

- CTLs or NK cell transfer for adoptive immuntherapy

Cell-based therapeutic vaccines

- Peptide-loaded DC used as tumor vaccines to induce immunity towards tumor-associated antigens
- Fused Tumor/DC hybrid cells

-> efficacy and endpoints of phase III efficacy clinical trials

Child in gene therapy programme develops leukaemia

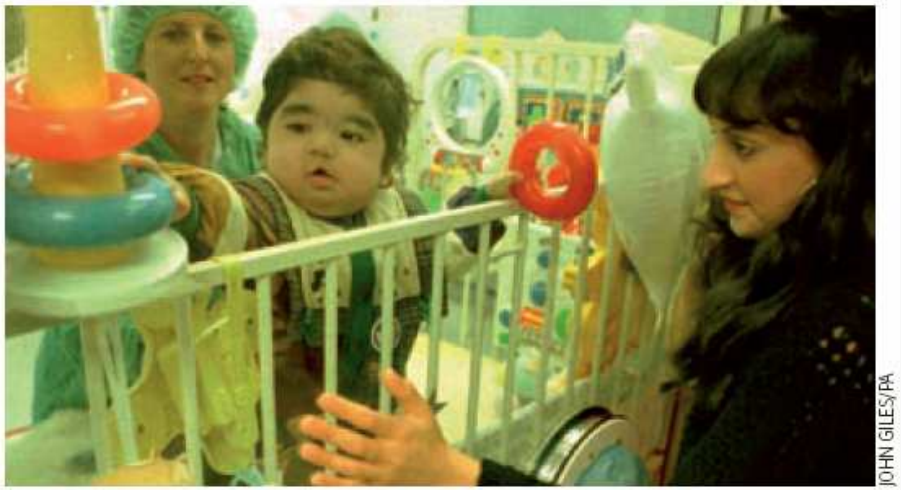
Andrew Cole LONDON

Doctors at Great Ormond Street Hospital for Children in London have admitted that other children may be at risk after leukaemia was diagnosed in a child on its pioneering gene therapy programme.

The unnamed 3 year old was taking part in a clinical trial treating children for X linked severe combined immunodeficiency (X-SCID), also known as "baby in the bubble syndrome," in which boys are born with no immune system. Around six to eight children are affected by the condition each year in the United Kingdom.

The trial, which began at Great Ormond Street in 2001 and ended earlier this year, involved 10 children with X-SCID and five with the related ada-SCID. Until now it seemed that most of the children had recovered successfully. However, four of 11 children involved in a similar trial in Paris were found, by 2002, to have gone on to develop leukaemia, one of whom died.

Bobby Gaspar, consultant immunologist on the London programme, admitted that other children taking part in the UK trial remained at risk. "Although we understand the mechanics of how this leukaemia happened, we can't say at this stage what the frequency will be."



JOHN GILES/PA

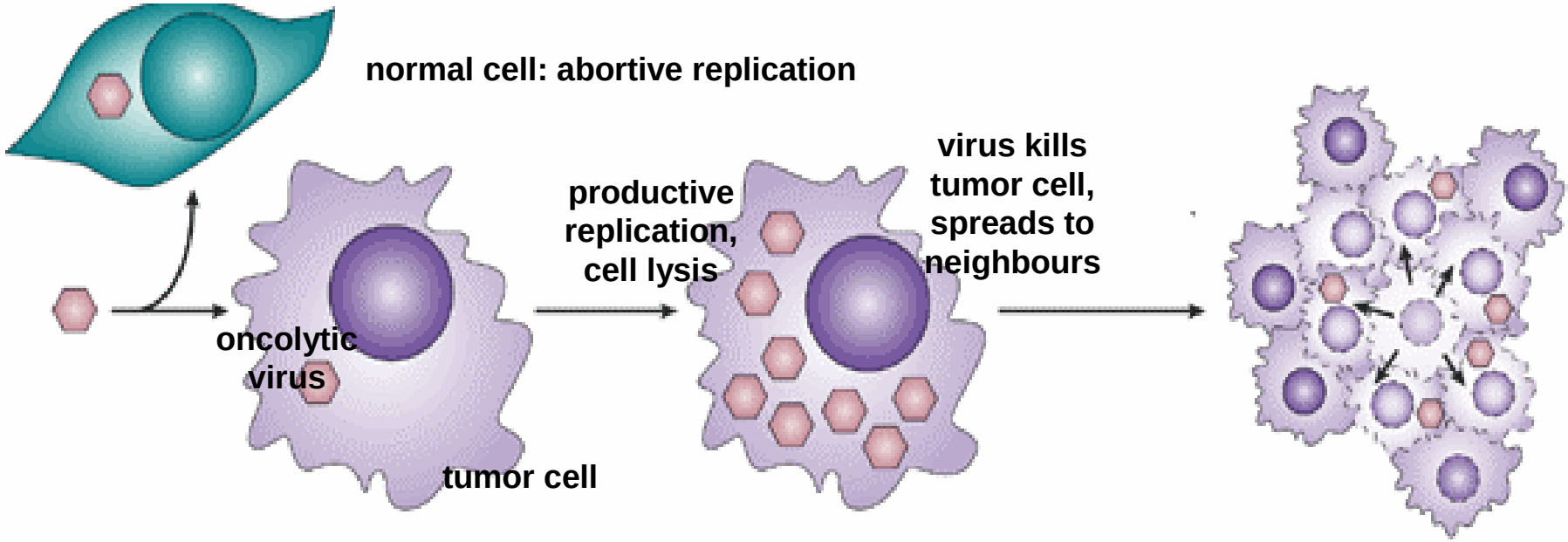
Aaron Nawaz, who lived in a protective bubble at a Newcastle hospital

Professor Gaspar insisted that all the families involved had been carefully counselled about the risks–including that of leukaemia once it was known–and none chose to pull out.

"You have to realise that these children are faced with a fatal disease," he said, "and they need to have some form of treatment." The conventional treatment was bone marrow transplantation, but if a full match wasn't possible the success rate was only 80%.

Conditionally replicating oncolytic virus: ICH Workshop Chicago (November 2005)

Virus engineered to direct their cytotoxicity towards cancer cells



Theoretical advantages:

- viral replication within tumor mass allows infection of additional cells
- lack of cross-resistance with standard therapies
- ability to cause tumor destruction by different mechanisms

Theoretical risks:

- introduction of new pathogens into the human population and adaptation

Gene therapy guidelines (EU, ICH)

CPMP/BWP/3088/99
Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products

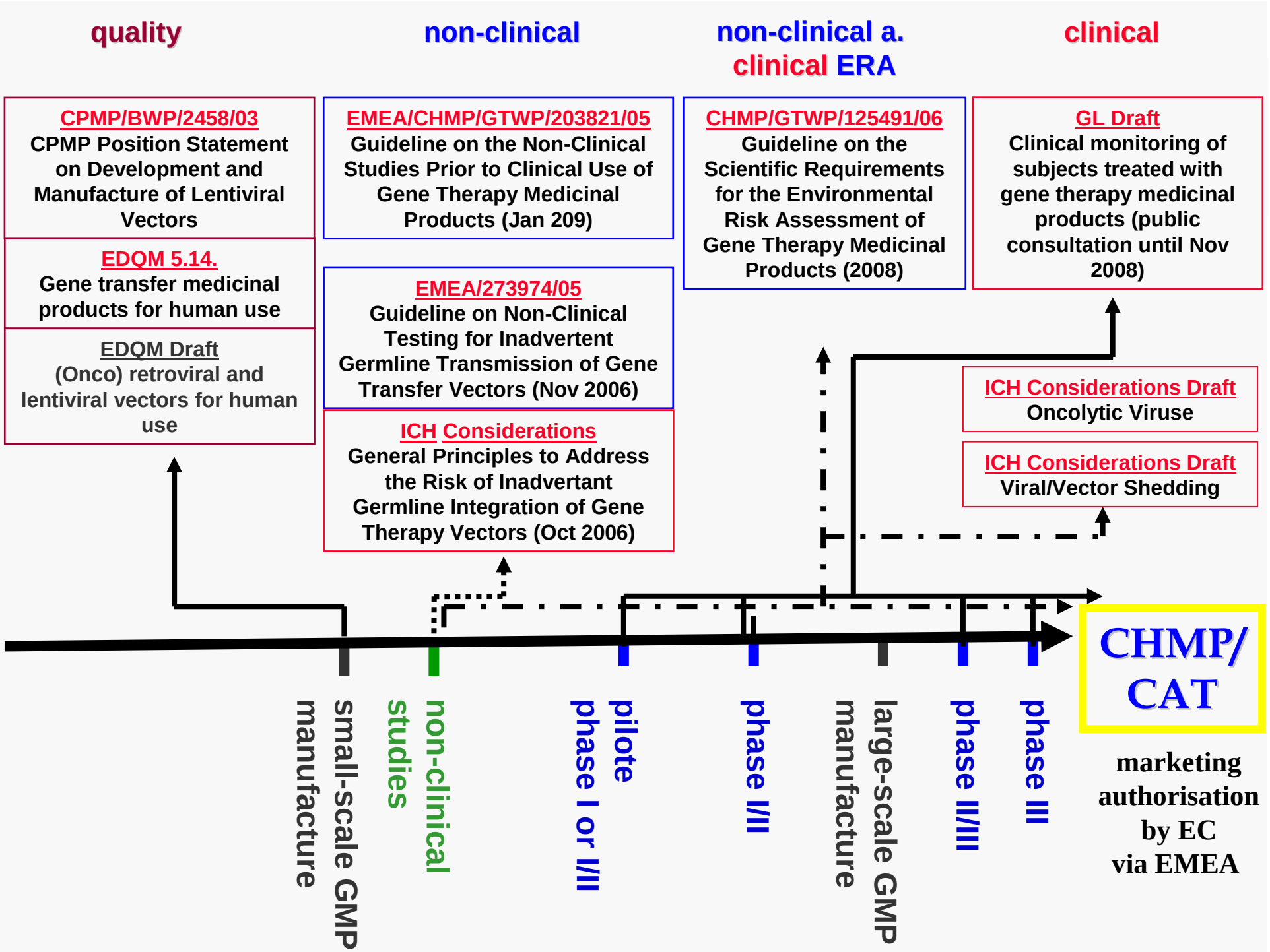
Parental EU gene therapy guideline

GL Draft
Guideline on Genetically Modified Cells

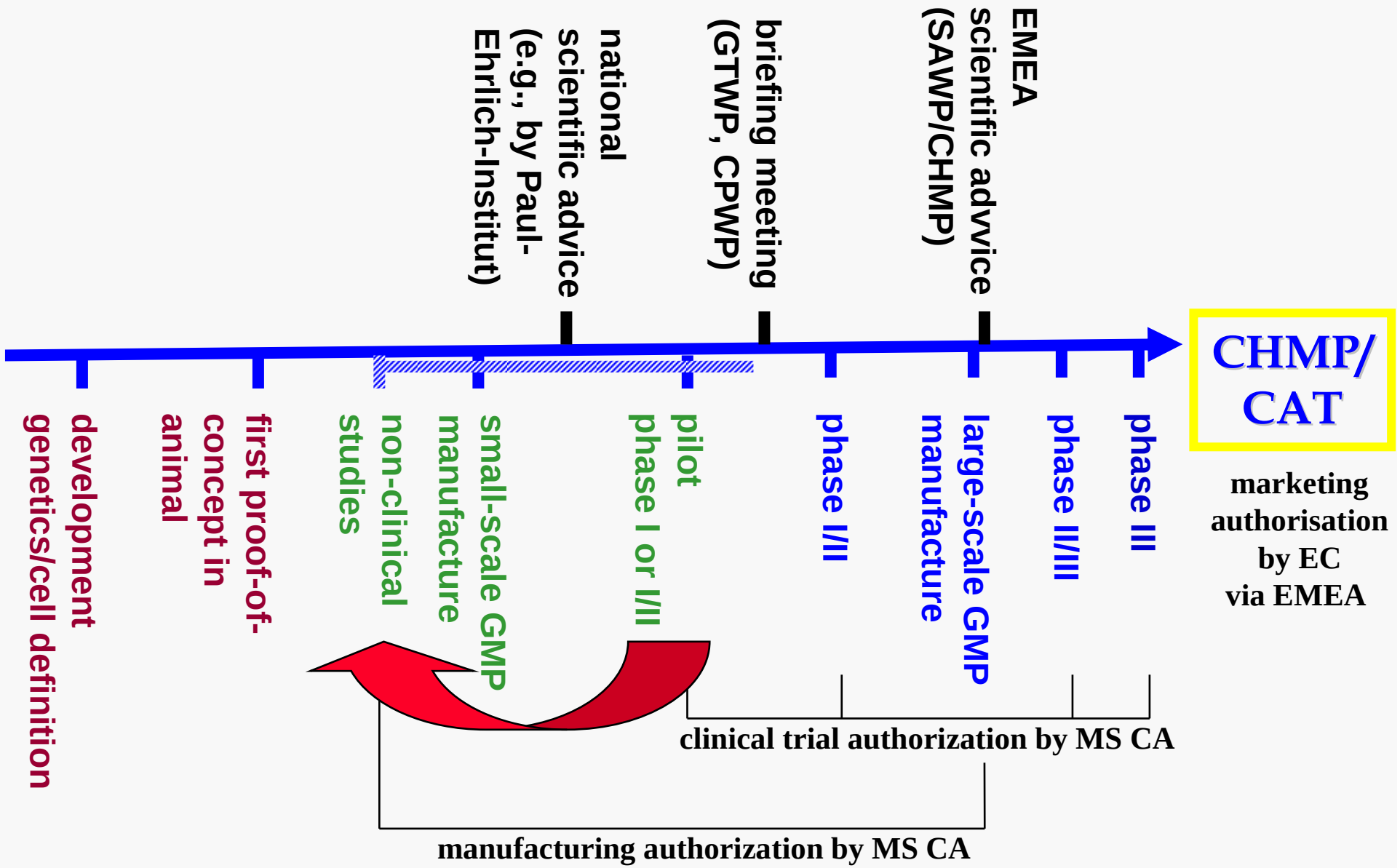
product-specific

GL Draft
Guideline on Live Vector and Recombinant Vaccines

CP Draft
Guideline on DNA Vaccines


quality
non-clinical
non-clinical a. clinical ERA
clinical
CPMP/BWP/2458/03
CPMP Position Statement on Development and Manufacture of Lentiviral Vectors
EDQM 5.14.
Gene transfer medicinal products for human use
EDQM Draft
(Onco) retroviral and lentiviral vectors for human use
EMEA/CHMP/GTWP/203821/05
Guideline on the Non-Clinical Studies Prior to Clinical Use of Gene Therapy Medicinal Products (Jan 209)
EMEA/273974/05
Guideline on Non-Clinical Testing for Inadvertent Germline Transmission of Gene Transfer Vectors (Nov 2006)
ICH Considerations
General Principles to Address the Risk of Inadvertant Germline Integration of Gene Therapy Vectors (Oct 2006)
CHMP/GTWP/125491/06
Guideline on the Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products (2008)
GL Draft
Clinical monitoring of subjects treated with gene therapy medicinal products (public consultation until Nov 2008)
ICH Considerations Draft
Oncolytic Viruse
ICH Considerations Draft
Viral/Vector Shedding
small-scale GMP manufacture
non-clinical studies
pilote phase I or I/II
phase I/II
large-scale GMP manufacture
phase II/III
phase III
CHMP/ CAT
marketing authorisation by EC via EMEA

Itinerary to ATMP development in the EU: free scientific advice and MAA review by EMEA



Safety and efficacy needs to be shown for ATMPs

Regulation (EC) No. 1394/2007:

The same regulatory principles apply as for other biotechnology MP

- quality, **safety and efficacy, ER**
- marketing authorisation
- post-authorisation vigilance & RMP

Clinical Development of ATMPs

Guideline on Human Cell-Based Medicinal Products

4.4.1 General aspects

- When a CBMP enters the clinical development phase the same principles as for other medicinal products apply. ... **a deviation from Phase I to Phase III clinical trials progression is acceptable but needs to be justified by the specificity of CBMP**.

The clinical development plan should include

- pharmacodynamic studies,
- pharmacokinetic studies,
- mechanism of action studies,
- dose finding studies,
- randomized controlled trials (RCTs)

Frequently asked question:
Is one radomized controlled trial sufficient for an MAA?

Is one randomized controlled trial sufficient?

Minimum requirement for one pivotal study (CPMP/EWP/2330/99 Points to consider on application with 1. Meta-Analysis; 2. one pivotal study)

- statistically compelling and clinically relevant results

Plan for more than 1 study when

- unknown mechanism of action
- new pharmacological principle
- phase I and II data limited
- new therapeutic area with history of failed studies or failures to confirm convincing results

Safety and clinical efficacy needs to be shown for ATMPs

- MAA can be applied for for orphan drugs based on a single clinical trial showing safety and efficacy

- In general a single pivotal phase III trial may suffice to support a MAA, but
- **statistically compelling and clinically relevant results required.**

- Primary endpoints usable
  - survival time (cancer)
  - alternatively: **validated** surrogate endpoints

    Example: Autologous chondrocyte implantation in the knee: Radiographic evidence by Magnetic Resonance Imaging (MRI) of cartilage repair may serve as surrogate for clinical outcome (if validated).

Current revision of Annex I to Dir. 2001/83/EC: dossier requirements for the MAA

- definitions — changes for GT MPs and SCT MPs, TEPs defined in AT MP Regulation
- Module 3: quality
  - GT MPs
  - SCT MPs incdlg. TEPs
- Module 4: nonclinical
  - GT MPs
  - SCT MPs incdlg. TEPs
- Module 5: clinical — GT MPs, SCT MPs, TEPs

Paul-Ehrlich-Institut

research topics

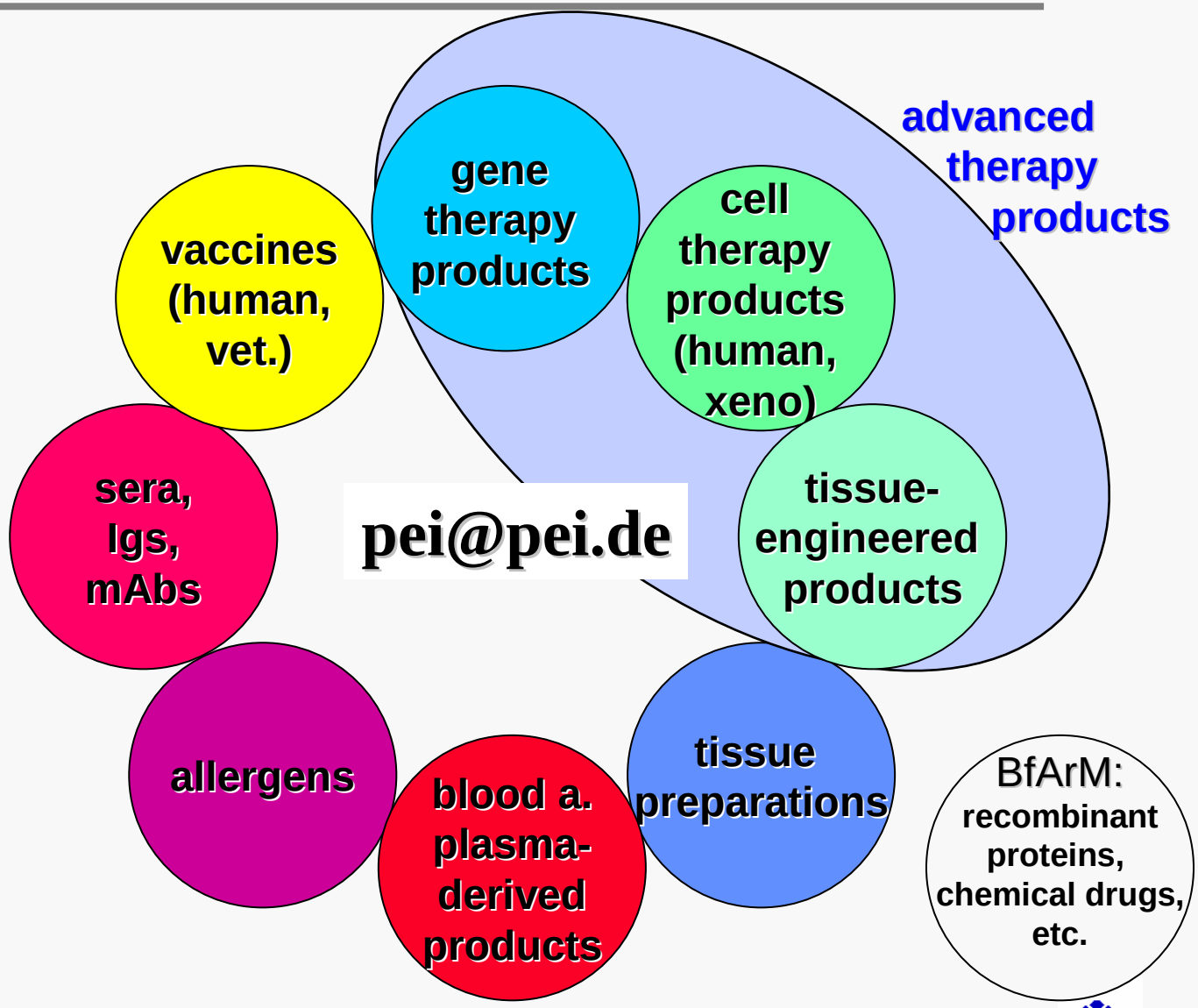
Safety and quality of biomedicines

Experimental therapy and diagnostics

Host interactions with pathogens and retroelements

Immune activation and evasion

medicinal product competence



15 min from Frankfurt Int. Airport

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines

Back-up slides

Module 3 (quality data requirements) of discussed new Annex I to Dir. 2001/83/EC (1)

- For gene therapy products, the general requirements for medicinal products apply unless divergence is adequately justified.

- Special attention shall be paid to the following items:
  - 3.2.1. Active substance
  - 3.2.1.1. Control of Starting materials
  - 3.2.1.2. Manufacturing process of the active substance(s)
  - 3.2.1.3. Characterisation of the active substance(s)
  - 3.2.1.4. Control of the active substance(s)
  - 3.2.1.5. Reference standards or materials
  - 3.2.1.6. Container and closure system of the active substance(s)
  - 3.2.1.7. Stability of the active substance(s)
  - 3.2.2. Finished medicinal product
  - 3.2.2.1. Description and composition of the finished medicinal product
  - 3.2.2.2. Pharmaceutical development
  - 3.2.2.3. Manufacturing process of the finished medicinal product
  - 3.2.2.4. Control of excipients
  - 3.2.2.5. Control of the finished medicinal product
  - 3.2.2.6. Reference standards or materials
  - 3.2.2.7. Container and closure of the finished medicinal product
  - 3.2.2.8. Stability of the finished medicinal product
  - 3.2.A.2. Adventitious agents safety evaluation

Module 4 (nonclinical data requirements) of discussed new Annex I to Dir. 2001/83/EC (1)

- **RISK ANALYSIS**
- The diversity of the group of Advanced Cell Therapy Medicinal Products means that the pharmaceutical development, non-clinical and clinical testing and the Risk Management Plans should be proportional/related to the risk expected from the product.
- A system of risk analysis is applied as an underlying principle which determines the extent of characterisation in terms of Quality, Nonclinical and Clinical data to be included in the Marketing Authorisation application dossier.
- Examples of risk factors are
  - the origin of the cells and/or the gene therapy medicinal product,
  - ability to proliferate and to differentiate,
  - ability to initiate an immune response,
  - level of cell manipulation,
  - mode of administration,
  - combination of cells with bioactive molecules or structural materials,
  - chromosomal integration of nucleic acid sequences,
  - their longterm functionality or oncogenicity.
- The availability of clinical data or experience with similar ATMP´s can also be considered.

Module 4 (nonclinical data requirements; GTMPs) of discussed new Annex I to Dir. 2001/83/EC (2)

- **Specific GTMP aspects**
- The appropriate level of nonclinical safety evaluation should be provided.

- *Viral vectors and genetically modified replicating micro-organisms and viruses*
- The rationale underlying the design of viral vectors - the use of replication-incompetent viral vectors or replicating micro-organisms and viruses- should be provided.

- *Genetically modified cells*
- The rationale underlying the use of the specific cell type, the use of the nucleic acid sequence introduced for their genetic modification and the result of the genetic modification should be provided.

- *Functional nucleic acid sequences*
- The rationale underlying the design of the nucleic acid sequence, and its functionality should be provided.

Module 4 (nonclinical data requirements; GTMPs) of discussed new Annex I to Dir. 2001/83/EC (4)

- *Toxicology*
- Toxicity of the gene therapy medicinal product shall be assessed, not only for the drug substance.
- Individual testing of drug components and excipients shall be taken into consideration, where appropriate.
- The in vivo effect of expression of nucleic acid sequence-related products not intended for the physiological function shall be evaluated.
- *Single-dose toxicity:* A single dose toxicity study should be conducted using the clinical route of administration and mode of application.
- *Repeated dose toxicity:* Studies shall be provided when multiple dosing of human subjects is intended. For those cases where single dosing may result in prolonged nucleic acid sequence functionality in humans repeated toxicity studies shall be considered. The application mode and scheme should closely reflect the planned clinical application. The duration of observations may be longer than in standard toxicity studies depending on the persistence of the gene therapy product.
- *Genotoxicity:* Standard genotoxicity studies are not generally required. However, genotoxicity studies may be required to address a concern about a specific impurity or a component of the delivery system.
- *Carcinogenicity/ oncogenicity/ tumorigenicity studies:* Standard life-time rodent carcinogenicity studies are not generally required. However, if an oncogenic potential of the gene therapy medicinal product may be assumed it should be evaluated in appropriate in vivo/in vitro models.

Module 4 (nonclinical data requirements; GTMPs) of discussed new Annex I to Dir. 2001/83/EC (5)

- *Reproductive and developmental toxicity:* Non-clinical germline transmission studies shall be provided, as appropriate.
- Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies shall be provided, if women of child-bearing potential or children are exposed to gene therapy product, unless the absence of such studies is justified.
- *Integration studies:* Integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germ line transmission. Nucleic acid sequence copy number per cell or tissue shall be taken into account for studies supporting dose definition.
- *Immunogenicity and immunotoxicity:* It is expected that immunological responses occur when an allogeneic or xenogeneic product is introduced. To address immunogenicity or immunotoxicity issues, the use of homologous models mimicking the clinical approach is recommended.
- Immunogenicity and immunotoxicity studies shall be provided for those gene therapy medicinal products that carry specific functions known to have an effect on the immune system. When an immunological response is intended against the gene therapy or nucleic acid sequence product, immunogenicity and immunotoxicity shall be investigated appropriately.
- Unexpected and undesirable consequences of long-term expression of a foreign antigen should be evaluated, as appropriate.

Module 5 (clinical data requirements) of discussed new Annex I to Dir. 2001/83/EC (3)

- For the deliberate release in the environment, attention shall be paid to the persistence of the Genetically Modified Organisms in the recipient and to the possible replication and/or modification of the Genetically Modified Organism when released in the environment.
- *Human Pharmacokinetic (PK) studies* shall include the following aspects:
- Shedding studies to address the excretion of the gene therapy medicinal product .
- Biodistribution of the vector, including distribution to gonads,.
- The pharmacokinetics of the transgene.
- *Human Pharmacodynamic studies* should address
  - the correlation between vector distribution,
  - the expression of the transgene and the therapeutic response.
  - The adequate dose to be used for efficacy studies should be defined on the basis of relevant functional and, as appropriate, structural parameters.
- *Safety studies* shall address the following aspects:
  - Emergence of replication competent vector
  - Potential for recombination or re-assortment
  - Release of endogenous virus in case of genetically modified cells
  - Risk of persistence of viral vector or latency
  - Risk of genomic integration and neoplastic proliferation due to insertional mutagenicity
  - immune response against all components of the gene therapy product

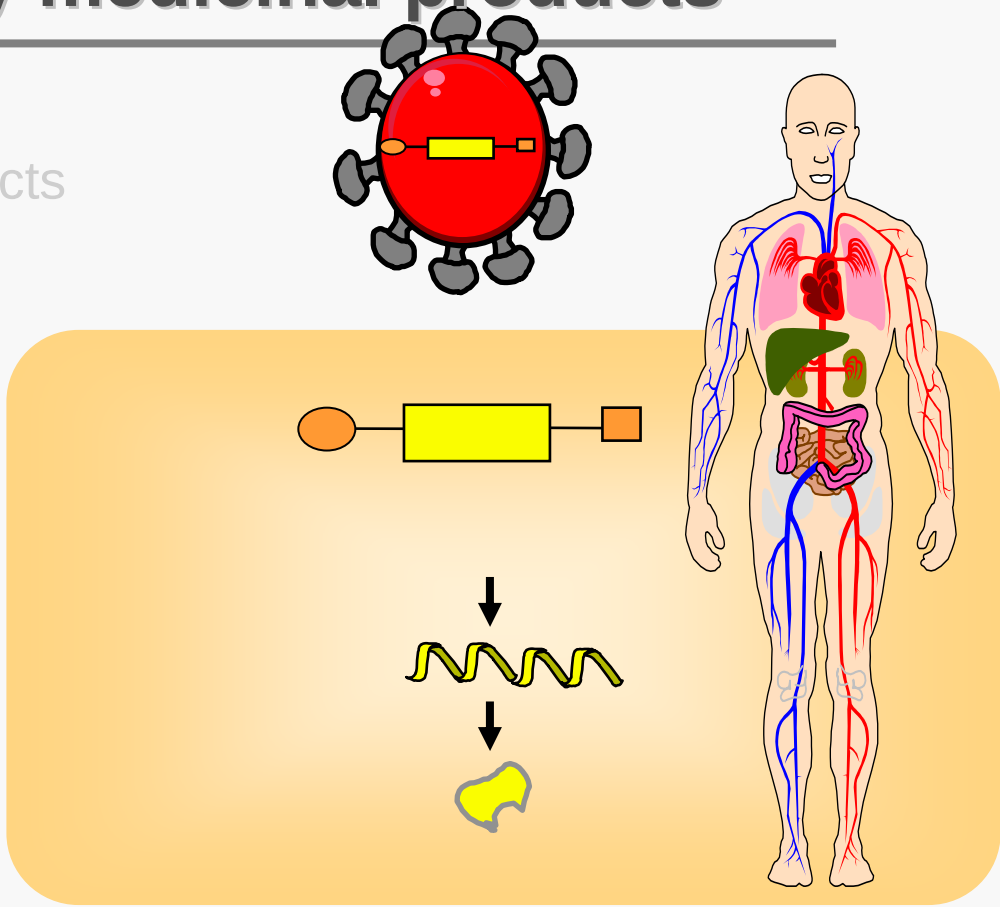
Module 5 (clinical data requirements) of discussed new Annex I to Dir. 2001/83/EC (4-1)

- For somatic CTMP whose primary mode of action is based on the production of active biomolecules, the study of the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules may be required.
- The biodistribution, persistence and long term engraftment of the CTMP components should be addressed during the clinical development.
- Safety studies shall address the following aspects were required:
  - distribution and engrafting following administration
  - ectopic engraftment
  - oncogenic transformation and cell/tissue lineage fidelity

- Pharmacokinetics
  - Conventional pharmacokinetics may not be relevant. However the biodistribution, persistence and long-term engraftment or degradation of the product should be evaluated early during clinical development. For somatic CTMP whose primary mode of action is based on the production of active biomolecules, the assessment of the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules may be required.

New legislation and regulations on advanced therapy medicinal products

- Regulation (EC) No. 1394/2007 on advanced therapy medicinal products
- Revision of Annex I to Directive 2001/83/EC
- CAT and guidelines developed by CHMP Working Parties on cell-based products and gene therapy



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The legal framework for tissues and cells has been provided

1 Legilsation addressing all Advanced Therapy Medicinal Products

- **Regulation 726/2004 (Mar 2004)**
  Centralized procedure via EMEA
- **Regulation on Advanced Therapy Medicinal Products (ATPs)**
  Definition of ATPs including TE products
  -> central licensing required
- **Directive 2001/83/EC (Nov 2001) amendend by 2003/63/EC (Jun 2003)**
  Community code relating to all medicinal products for human use
  Technical requirements with a view to licensing

1 + 2 Legislation on Tissues & Cells, addressing all cell-containing products

- **Directive 2004/23/EC (Mar 2004)**
  setting standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues/cells

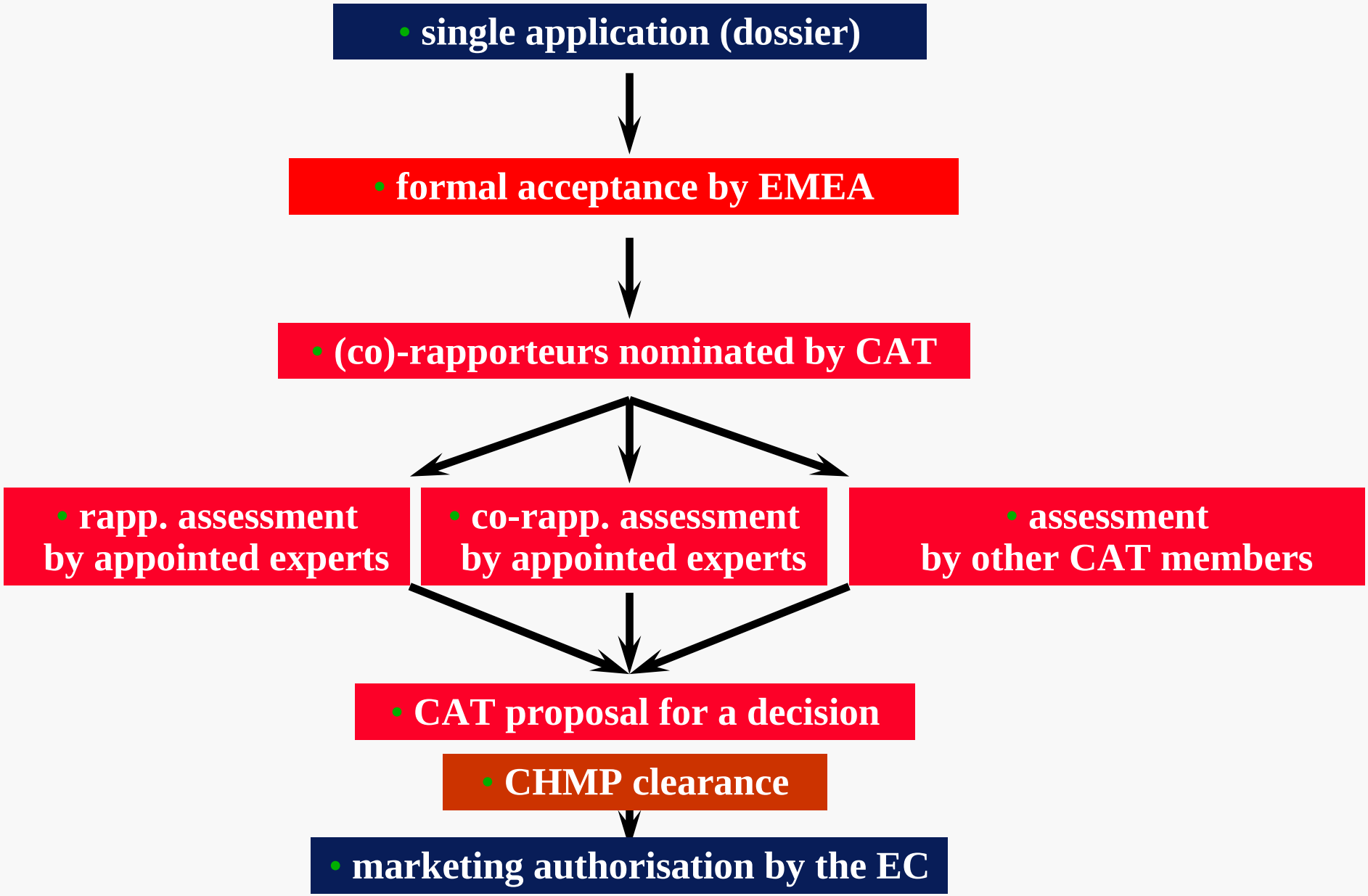
2 Technical Requirements for tissues and cells

- **Directive 2006/17/EC**
  technical requirements for donation, procurement and testing
- **Directive 2006/86/EC**
  technical requirements for coding, processing, preservation, storage, distribution

3 Guidelines

- **Guideline on cell-based products including TEPs (2008 until present)**
- **Note for guidance on…gene transfer medicinal products and related guidance (2003 until present)**

The centralized MA allows SMEs with small and individual products to enter the pan-EU market



Gendux gibt bekannt, dass der Marktzulassungsantrag für sein Medikament ADVEXIN von der EMEA zur Überprüfung angenommen wurde

DUBLIN--(BUSINESS WIRE)--Gendux Molecular Limited („Gendux”) gab heute bekannt, dass sein Marktzulassungsantrag (Marketing Authorization Application = „MAA”) für ADVEXIN® („Contusugene Ladenovec”) von der Europäischen Arzneimittelagentur („EMEA”) zur fachlichen Überprüfung angenommen wurde. ADVEXIN® dient zur Behandlung einer Form des hereditären Krebses, dem Li-Fraumeni Syndrom („LFS”). Wie Gendux verkündete, war dessen MAA für ADVEXIN am 13. November 2007 bei der EMEA eingereicht worden. ADVEXIN ist die erste Therapie, die speziell auf ein vererbbares Krebbsyndrom ausgerichtet ist. Die Wirkung von ADVEXIN besteht in der Umkehrung eines der häufigsten genetischen Krebsdefekte, Anomalien der p53 Tumorsuppressor-Werte, die bei Li-Fraumeni-Patienten vererbt sind und in der Mehrzahl der nicht-vererbbaren Krebserkrankungen vorkommen. ADVEXIN wird darüberhinaus als Therapie für Kopf- und Nackenkrebs entwickelt; die Eingaben für diese Indikation werden sowohl in Europa als auch in den USA vor Ende des Jahres 2007 erwartet.
Die Genehmigung des MAA für ADVEXIN wird die behördliche Überprüfung der präklinischen und klinischen Daten, sowie der Herstellungsdaten des Antrags durch die EMEA einleiten.

New legislation and regulations on advanced therapy medicinal products

- Regulation (EC) No. 1394/2007 on advanced therapy medicinal products
- Revision of Annex I to Directive 2001/83/EC
- CAT and guidelines developed by CHMP Working Parties on cell-based products and gene therapy

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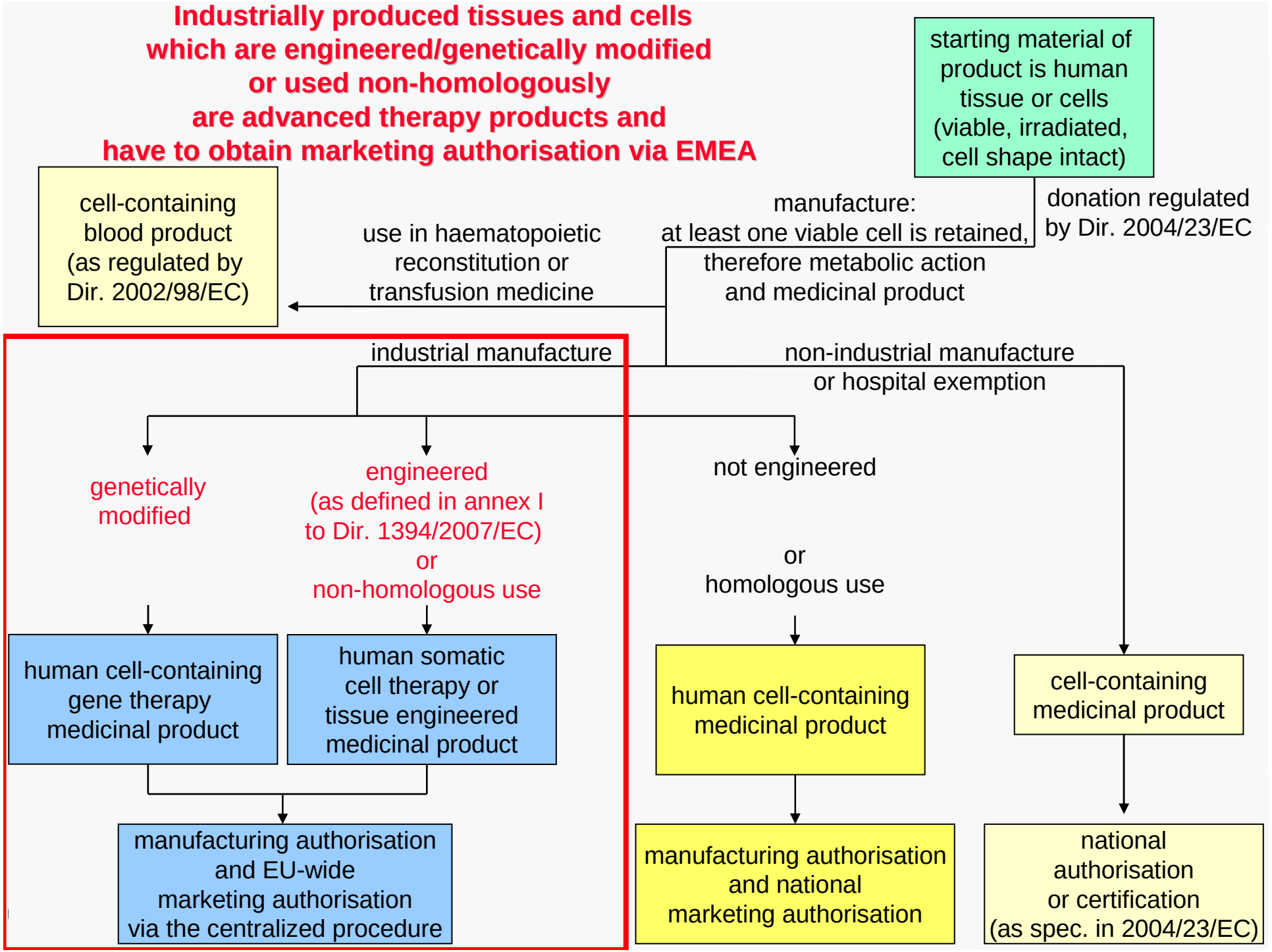
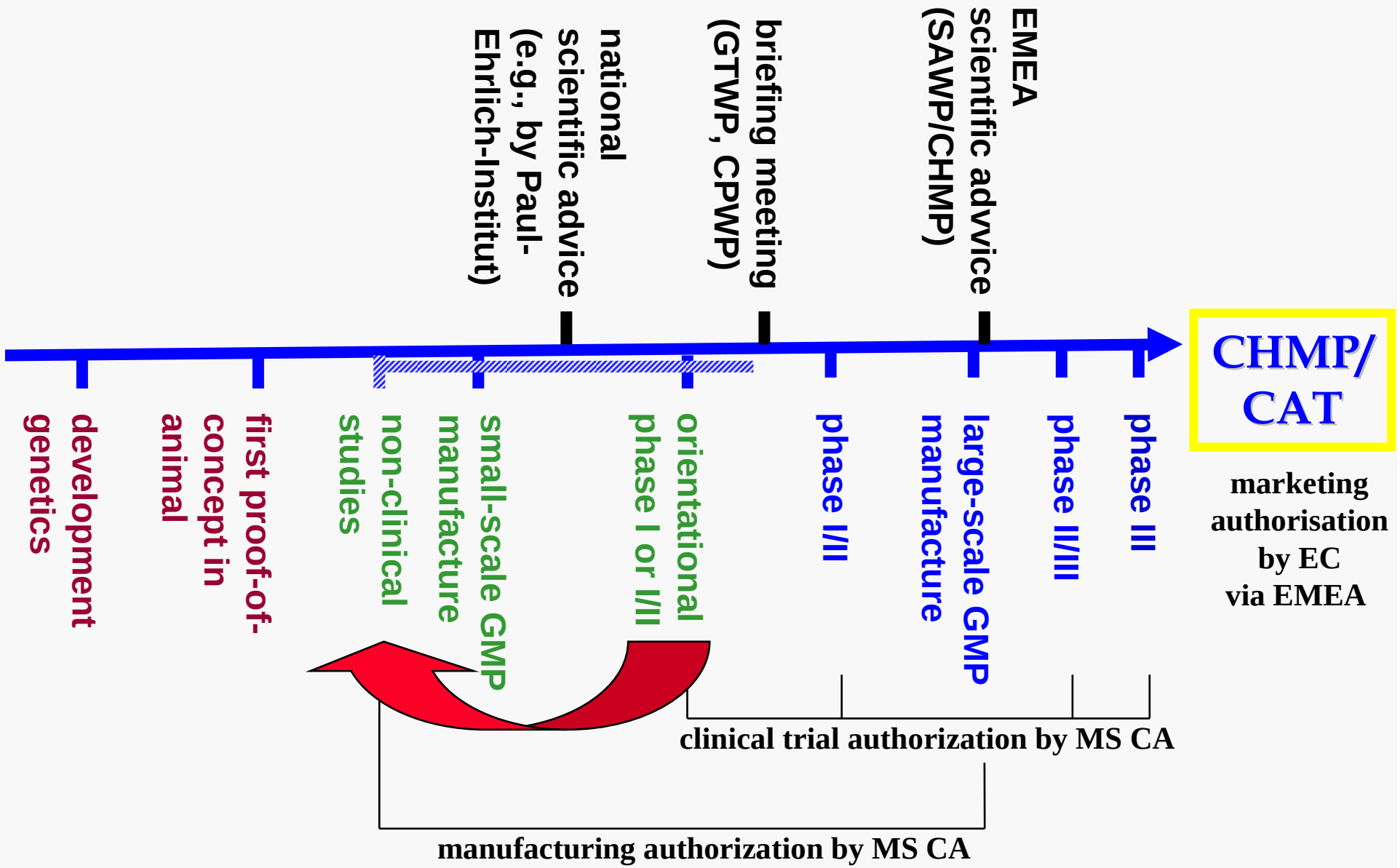

Industrially produced tissues and cells
which are engineered/genetically modified
or used non-homologously
are advanced therapy products and
have to obtain marketing authorisation via EMEA
starting material of product is human tissue or cells (viable, irradiated, cell shape intact)
donation regulated by Dir. 2004/23/EC
manufacture:
at least one viable cell is retained,
therefore metabolic action
and medicinal product
cell-containing blood product (as regulated by Dir. 2002/98/EC)
use in haematopoietic reconstitution or transfusion medicine
industrial manufacture
non-industrial manufacture or hospital exemption
genetically modified
engineered (as defined in annex I to Dir. 1394/2007/EC) or non-homologous use
not engineered
or homologous use
human cell-containing gene therapy medicinal product
human somatic cell therapy or tissue engineered medicinal product
human cell-containing medicinal product
cell-containing medicinal product
manufacturing authorisation and EU-wide marketing authorisation via the centralized procedure
manufacturing authorisation and national marketing authorisation
national authorisation or certification (as spec. in 2004/23/EC)

Reiterative phase I trials mark the beginning of ATMP development and informal briefing meetings are needed



How will we scope with individually prepared products for very few patients?

- Will a small phase I/II study be acceptable for MA?
- Can we classify the small-scale individual production as industrial manufacture?
- Do GMP and GCP requirements need special adaptation to small-scale ATMP production?

Reasons for regulatory classification are the resulting regulatory and procedural consequences

- Advanced therapy medicinal products (AT-MPs) contain or consist of
  - intendedly manipulated cells resulting in substantial alteration of their biological characteristics (hSCT-MPs)
  - “engineered” cells (TEPs)
  - vectors (viral, non-viral, naked DNA), replicating (oncolytic) viruses, vector-containing cells (gene therapy MPs)
  - Xenogeneic cells (xenogeneic cell therapy MPs).

- As a consequence of being classified as SCT-MPs, it is necessary
  - to obtain marketing authorisation for use in standard therapy
  - via the centralised procedure (coordinated by CAT/CHMP at EMEA),
  - which is a marketing authorisation for all EU member states via a single application to the European Medicines Agency (EMEA),
  - to undertake clinical trials under GCP intended to collect data for marketing authorisation have to be done (authorisation within 90 days),
  - to obtain manufacturing authorisation including GMP,
  - to undertake some non-clinical pharmacological-toxicological studies under GLP.

Avanced Therapy Clinical Trial Applications in the EU since August 2004 (20.08.2007, EudraCT)

clinical use	number
Gene therapy/transfer MPs	*67 trials / 33 original products*
cancer	19
cardio-vascular	4
autoimmune diseases	2
HIV vaccine	2
infectious disease (chronic hepatitis C)	1
neuronal	2
vaccines (monovalent, combi-)	3
Biologicals (EU)	*5977*

Avanced Therapy Clinical Trial Applications in the EU since August 2004 (20.08.2007, EudraCT)

clinical use	number
Somatic cell therapy MPs	*120 trials / 101 original products*
cancer immunotherapy	39
cardio-vascular	29
skin/liver/lung/eye/diabetes/intestine/bone TE	25
neurological	5
lymphohistiocytosis (HLH)	1
AIDS	1
infertility	1
Biologicals (EU)	*5977*

Advanced Therapy Medicinal Products: Present and Future Regulation in the EU

- Advanced Therapy Medicinal Products
- Are we prepared?
- What will be the product-related issues?

Ready for action: custom-made gene vectors are held for use in a gene-therapy trial.

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Viseu, 20 November 2007

Aims of non-clinical studies prior to first clinical use: preventive vaccine

- Studies should be designed and carried out aiming at establishing the following:
  - functionality and proof-of-concept in non-clinical model(s)
  - release of biologically active molecules
  - maintenance of the intended phenotype and absence of pre-neoplastic changes
  - biodistribution and half-life in the living organism
  - recommendation on initial dose and dose escalation scheme to be used in the proposed clinical trial (max. feasible dose)
  - identification of potential mechanisms and target organs of toxicity
  - identification of parameters to be monitored in the proposed clinical trial
  - identification of patient eligibility criteria

Changes accrdg. to the EC ATMP Proposal

- Centralized licensing procedure for all ATMPs
  - Gene therapy products
  - Human somatic cell therapy products
  - Xenogeneic somatic cell therapy products
  - Tissue engineered products
- Autologous and directionally used medicinal products will undergo licensing
  - cell banks
  - industrially produced
- Tissue engineered products and somatic cell therapy products will undergo central licensing,
  - live (viable) and
  - substantially altered or engineered ????

Short list of pre-requisites for a first clinical trial (1)

- Established manufacturing method
- Validated manufacturing process according to GMP
- Setting of rational and state-of-the-art product acceptance criteria
  - for the active substance and
  - for contaminants (from cell substrate or from culture media)
    - proteins
    - DNA
    - specific cell genes (e.g., oncogenes) or gene products from cell substrate
- Evidence for intended mechanism in animals
- Single (and repeated) dose toxicity tested (GLP)
  - organ toxicity/biodistribution/half-life
  - auto-immune disease
- Local tolerance if applicable

Short list of pre-requisites for a first clinical trial (2)

- Established first dose
- Established maximum tolerated or maximum feasible dose
- Dosing regimen
- Clinical trial design, statistics
- Inclusion/exclusion criteria
- Medical interventions
- Tests and medical interventions planned during the clinical trial
- Patients´ follow-up, if applicable
- Investigator´s brochure
- Patient information leaflet

Innovative biotechnology medicinal products

Gene Transfer Medicinal Products	(vectors, DNA, gen. mod. cells, micro-org.)
Somatic/Xenogeneic Cell Therapy MPs	(human cells; immunotherapy)
Tissue Engineering MPs	(human cells incldg. stem cells)
Tissue Preparations	(human sinews, valves, bones,…)

Paul-Ehrlich-Institut

Medical Biotechnology

Licensing, scientific advice

Dev. of NfGs (EMEA)

CHMP Gene Therapy WP (EMEA/CHMP)

WHO Clinical Gene Therapy Monitoring Group

Clinical trial, manufacture

Commission of Somatic Gene Therapy

Clinical trial approval

Inspections

Basic scientific research

Retrovirology	(HIV / SIV and HERV / PERV)
Gene therapy	(AIDS and tumor gene therapy)
Cell therapy/TE	(Signal transduction, stem cell diff.)

Cell-based product guideline: General credo of non-clinical development

- Objectives of non-clinical studies
  - demonstrate proof-of-principle
  - define pharmacological and toxicological effects to be expected during human use
  - select a safe dose for human use
  - support route of administration and application schedule
  - measure duration of exposure (half-life of cells and their effect in vivo)
  - define reasonable follow-up time to detect adverse reactions
  - detect target organs of toxicity and parameters for patient monitoring in subsequent clinical trials
- Use relevant animal models and justify:
  - Expression level of biologically active molecules,
  - route of administration,
  - dosage…
    - …should reflect the intended human use.
- Consider ICH S6 Guideline on the safety of biotechnology-derived pharmaceuticals
- Demonstrate safety and suitability of all components for all intended functions.

Cell-based product guideline: primary pharmacodynamics of cells (1)

- Use reasonably justified markers of pharmacodynamic action in vivo
  - Cells used to substitute for functions of deficient cells or tissues
    -> Measure these cell functions and body function restoration in vivo and in vitro.
  - Cells used for adoptive immunotherapy or vaccination in cancer patients
    -> Use immune assays capturing the intended immunological effect.

- Homologous animal model use
  - may be advantageous to mimick the human situation more closely,
  - should be considered to study stem cell differentiation.

- Use in vitro studies to address
  - cell and tissue morphology,
  - proliferation,
  - phenotype,
  - heterogeneity and
  - the level of differentiation.

Cell-based product guideline: primary pharmacodynamics of cells (2)

- Determine minimal or optimal cell amount to be administered for achieving the desired effect:
  - cell number,
  - cell concentration,
  - required cell characteristics
    - stage of differentiation,
    - heterogeneity required or tolerated).

Cell-based product guideline: secondary and safety pharmacodynamics of cells (2)

- Secondary pharmacodynamics:
  Investigate potential undesired effects of the cell-based product:
  - homing to other than the intended organs,
  - secretion of other bioactive molecules beside the protein(s) of interest,
  - undesirable effects of the protein(s) of interest,
  - undesirable targets of the protein(s) of interest.

- Safety pharmacodynamics:
  Due to secretion of pharmacologically active substances from cells, there may be
  - CNS dysfunctions,
  - cardiac dysfunctions,
  - respiratory dysfunctions,
  - renal dysfunctions
  - gastrointestinal dysfunctions.

- Watch ICH S7A Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00), when applicable.

Cell-based product guideline: kinetics, migration persistance of cells (3)

- Conventional ADME studies are genrally not relevant.

- Relevant are measurements of
  - tissue distribution,
  - viability,
  - trafficking,
  - growth,
  - phenotype and
  - any alteration of phenotype due to factors in the new environment.

Cell-based product guideline: kinetics, migration persistance of cells (4)

- Conventional ADME studies are generally not relevant.
- Relevant are measurements of
  - tissue distribution,
  - viability,
  - trafficking,
  - growth,
  - phenotype and
  - any alteration of phenotype due to factors in the new environment.
- With respect to produced systemically active biomolecules. study
  - the distribution,
  - duration and
  - amount of expression of these molecules and
  - the survival and
  - the functional stability of the cells at target sites.

Cell-based product guideline: interactions (5)

- Study interaction of all componénts including the non-cellular structural ones with
  - the surrounding tissue.

Cell-based product guideline: toxicology (6)

- Toxicity may evolve, for example,
  - due to unknown cellular alterations developing during the manufacturing process
    - such as altered excretion patterns and
    - altered in vivo behaviour due to differentiation,
  - due to allogeneic product use
  - the presence of components
    - that are used in the manufacturing process or
    - are part of a structural component,
  - or proliferation of the applied cells
    - in an unwanted quantity or
    - in an unwanted location.

Cell-based product guideline: toxicology (7)

- Conventional toxicology studies might nevertheless be required, for example
  - for complex regimens where CBMP are combined with other medicinal products or treatments
    - such as adjuvants/cytokines or irradiation, respectively.

- The need for drug interaction studies is dependent on the intended use and the type of the cell-based product and should be discussed.

- The induction of an immune response
  - against the cells themselves and/or
  - towards cell-derived pharmacologically active substances

    -> might modulate the efficacy of the CBMP.
    ->The possible immunogenicity of a CBMP should be considered.
  - For guidance on immunogenicity of excreted substances see ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

- Auto-immunity should be considered when cells are used for immunotherapy purposes, e.g. cancer immunotherapeutic products.

Cell-based product guideline: other non-clinical studies (8)

- Single and repeated dose toxicity:
  - relevant animal model where cells should not immediately be rejected,
  - combine with safety pharmacology, local tolerance, or proof of concept and efficacy studies.
  - Use homologous model for autologous use.

  - The duration of observations might be much longer than in standard single dose studies,
    - since the cells are supposed to function for long times,
    - which should be reflected in the design of these studies.
    - The route and dosing regimen should reflect the intended clinical use.

- Repeated dose toxicity studies are only relevant if the clinical use includes multiple dosings.

Cell-based product guideline: other non-clinical studies (9)

- Local tolerance
  - may be required (e.g., for i.d. administered cell-based cancer vaccines),
  - to be carried out in appropriate species
  - Combine, if possible, in single or repeated dose toxicity studies
    - local tolerance,
    - tissue compatibility and
    - tolerance to excreted substances can be evaluated.

- Tumourigenesis due to neoplastic transformation
  - of host cells,
  - of the cells in the CbMP;
  - preferably to be performed with cells that are
    - at the limit of routine cell culturing or
    - even beyond that limit.
  - Tissues found to contain applied cells or expressed products during the biodistribution studies should also be analysed with special emphasis during tumourigenicity studies.

Cell-based product guideline: other non-clinical studies (10)

- Carcinogenicity studies:
  - should be considered;
  - conventional studies may not be feasible.
- Genotoxicity studies
  - None,
  - unless secreted substance or molecule may interact with DNA/chromosome.
- Reproductive studies
  - Depending on use.

Cell-based product guideline: cliinical development (11)

- The clinical development plan should include
  - pharmacodynamic studies,
  - pharmacokinetic studies,
  - mechanism of action studies,
  - dose finding studies and
  - RCTs
  - in accordance with the existing general guidances and specific guidances for the condition evaluated.

- Risk Management Plan:

  The long-term safety issues should be addressed, such as
  - infections,
  - immunogenicity/immunosuppression,
  - malignant transformation,
  - durability of the associated medical device/biomaterial component.

Directive 2006/17/EC
of the European Commission of 8th Feb 2006

Implementing 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

ANNEX II Laboratory tests for ALL donors of tissues/cells (except reproductive cells) <u>including</u> autologous donors when cells are stored or cultured

HIV-1/-2	**anti-HIV-1/2**	
HBV	**HBsAg** **anti-HBc**	**further tests when anti-HBc$^+$ and HBsAg$^-$**
HCV	**anti-HCV-Ab**	
Syphilis	**validated specific or non-specific test**	
HTLV	**anti-HTLV**	**only for high-risk donors**
RhD, HLA, Malaria CMV, Toxoplasma, EBV, Trypanosoma cruzi		**„may be required“**

- test on serum/plasma
- qualified/authorized lab
- validated tests

Advanced therapy medicinal products

- Classification
- New procedures and guidelines
- Product-specific considerations

Calculated risk: the use of viral vectors to deliver corrective genes to a patient can cause side effects.

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Bonn, 17 June 2008

Safety and clinical efficacy needs to be shown for ATMPs

- Orphan drugs can apply fo marketing based on a single clinical trial showing safety and efficacy

- A single pivotal phase III trial may suffice to support a MAA,

  - Product vs. placebo not possible due to ethical considerations
  - Product vs. standard practice of care
  - Product alone

- Hard endpoints usable
  - survival time (cancer)
  - Inclusion of patients without other treatment option
  - validation of biomarkers
  - secondary endpoints: clinical benefit, time until conventional treatment