資料3－2

Regulatory requirements for cell based medicinal products

Committee

25 August 2010

Dr. Bettina Klug, MSc
Paul-Ehrlich-Institut, Langen

klube@pei.de

Paul-Ehrlich-Institut
Federal Institute for Vaccines and Biomedicines

Centralised Procedure

Rapid and EU-wide authorisation for innovative medicines (210 days)

1 **evaluation**

1 **authorisation**

1 **product information (SPC, Labelling, PL)**

22 **languages!**

Regulatory framework

Regulation (EC) No 726/2004

Scope

- Biotechnology Products (Art 3 (1) and point 1 of the Annex)
  - Controlled gene expression (e.g. "transgene")
  - r-DNA
  - MABs
  - Gene therapy
  - Somatic cell therapy
    (Not Tissue engineered products)
- New active substance
- Orphan medicinal products

Regulation (EC) No 1394/2007

- ✓ Amendment to Annex 1 (Directive 2003/63/EC)
- ✓ Traceability
- ✓ Long-term follow up of safety and efficacy
- ✓ Incentives
  - ✓ Scientific Advice on PhV and RMP
  - ✓ Fee Reductions (SMEs)
  - ✓ Scientific recommendation on ATMP classification
  - ✓ Certification of quality and non-clinical data

- ✓ Establishment of CAT

- ✓ Transitional Period
  - ➢ Until 30 December 2011
  - ➢ Until December 2012 (TEPs)

Regulation (EC) No 1394/2007
Chapter 1 Article 2

(b) Tissue engineered products

- engineered cells or tissues, and
- regenerating, repairing or replacing a human tissue

Î 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

Regulation (EC) No 1394/2007
Chapter 1 Article 2

- **(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**

Regulation (EC) No 1394/2007
Annex 1

Manipulations not considered as substantial manipulations:

- Cutting
- Grinding
- Shaping
- Centrifugation
- Sterilization / irradiation
- Filtering / lyophilisation
- Cell separation, purification, concentration
- Freezing / cryopreservation
- Soaking in antibiotic /antimicrobial solutions

Directive 2001/83/EC
Annex 1

Part IV Advanced Therapy Medicinal Products

Somatic cell therapy medicinal products

- For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).

Regulatory framework
-Cells and Tissues-

- **Directive 2004/23/EC**

  Standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissue/cells

- **Directive 2006/17/EC**

  Technical requirements for donation, procurement testing

- **Directive 2006/86/EC**

  Traceability, notification of serious adverse reactions and events, technical requirements for coding, processing, preservation, storage distribution

Regulatory framework
-Cells and Tissues-

- Guideline on human cell-based medicinal products (EMEA/CHMP/410896/2006)

- Concept paper on the development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (CHMP/CPWP)708420/09)

- Reflection paper on stem cell-based medicinal products (CAT/571134/09)

GCP legislation

📖 Directive 2001/20/EC

- The applicant has provided a statement that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC

📖 Directive 2005/28/EC

- ✓ Art 1 (1) The rights, safety and well being of the trial subjects shall prevail over the interest of science and society

GCP Definition (ICH)

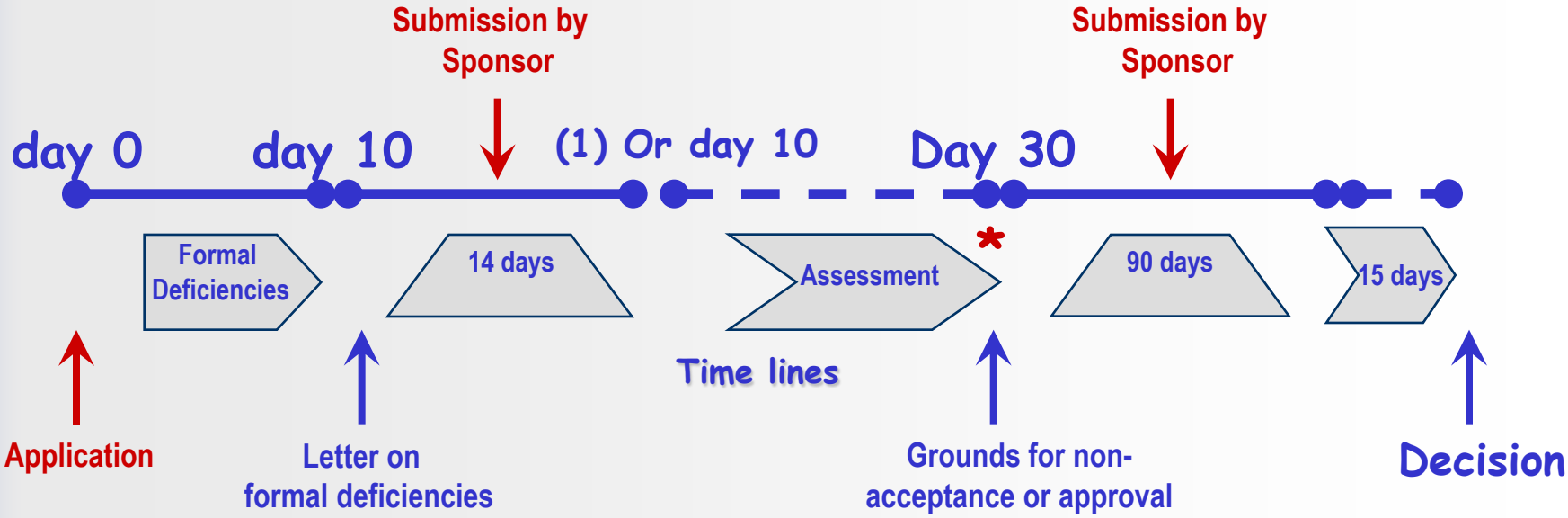
An international ethical and scientific quality standard for designing, conducting and reporting clinical trials …… to ensure the rights, safety and well-being of trial subjects are protected

- **Rights, integrity and confidentiality of trial subjects are protected**

and

- **Data and reported results are credible, and accurate**

Clinical trial application (DE)



Biological Products (human or animal origin)	60 Days
Somatic Cell-Therapeutics; Gene Therapy Products Genetically modified Organisms (GMO)	90 Days
Xenogene Cell-Therapeutics	No time-limit

* Vaccines; Allergens; Biotech. acc. Reg. 726/2004/EC

Voluntary Harmonisation Procedure (VHP) for clinical trials

VHP

- ✓ Clinical trial is planned to be carried out in three or more Members States
- ✓ Subsequent substantial amendments will also be handled by the VHP

  - ➢ Single application
  - ➢ Single evaluation (written in english)
  - ➢ Single list of questions (protocol, IMP)

  ➔Clinical trial authorisation (NCA) within 10 days

Voluntary Harmonisation Procedure (VHP) for clinical trials

Eligibility criteria

- ✓ Clinical trial is planned to be carried out in three or more Members States
- ✓ Subsequent substantial amendments will also be handled by the VHP
- ✓ The harmonized scientific assessment will start immediately following submission of a single application (written in English)

Clinical trial requirements
Quality, non-clinical

- **Quality**
  - ✓ **Manufacturing procedure (GMP certificate)**
  - ✓ **Impurities / Specifications**
  - ✓ **Excipients, adventitious agents**

- **Non-clinical**
  - ✓ **Proof of concept**
  - ✓ **Safety / toxicity (GLP)**

Support

EMA

- **Briefing meetings**
- **Scientific Advice / Protocol Assistance**
- **Regulatory Advice**
- **Certification**

- **SME**

www.ema.europa.eu

Support

PEI - Innovation Office

- **Coordination of national Scientific Advice**
- **Regulatory Advice**
- **Preparation of SME status**

innovation@pei.de

www.pei.de

Thank you for your attention