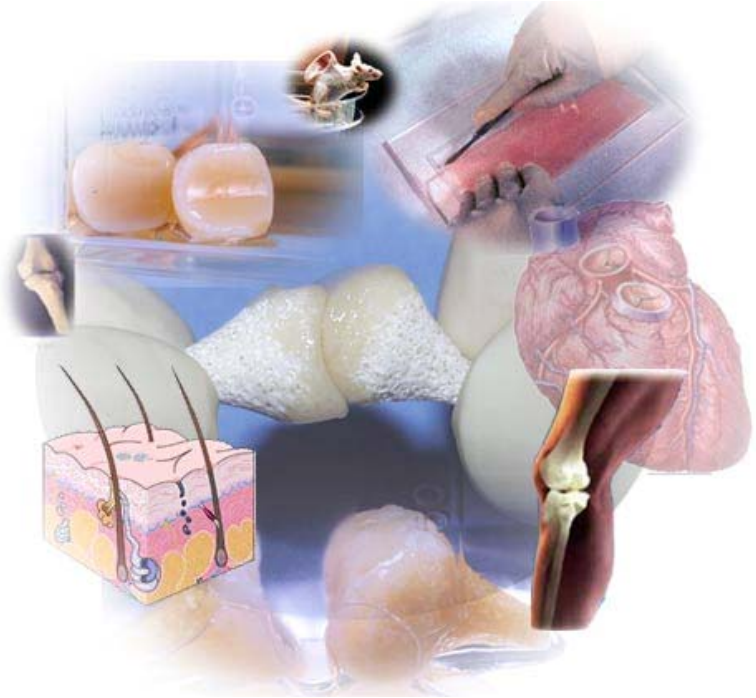
FIRST WORKSHOP ON ADVANCED THERAPY MEDICINAL PRODUCT

London, 3 April 2009

Afternoon session

- **During the morning, you were informed about**
  - » ATMP Regulation & its implementation
  - » CAT
  - » Procedures for Evaluation of ATMP
  - » Certification of Quality/Non-clinical data
  - » Scientific recommendation on classification
- **This afternoon, we will address**
  - » New Annex I
  - » Dossier requirements for:
    - – Cell-based MP (somatic CTMP and TEP)
    - – Gene therapy MP
  - » Post-authorisation follow-up and traceability

Technical requirements for Advanced Therapy Medicinal Products in Annex I



First Workshop on ATMP

3 April 2009

Patrick Celis

Current Annex I

- **Annex I, Part IV to Directive 2001/83/EC already describes the dossier requirements for**
  - » Gene therapy products
  - » Somatic cell therapy products

- **… and includes the definitions of a gene therapy and somatic cell therapy product**

- **Requirements established in 2003 (Directive 2003/63/EC amending Directive 2001/83/EC)**

Procedure for revision (1)

- **EMEA (via CHMP and its WPs) prepared a technical contribution to Commision for the revision of Annex I Part IV**
  - » Risk based approach
  - » New definitions GTMP and sCTMP
  - » Updated requirements (Q/N-C/C) for GTMP and sCTMP
    - – Experience with those products
    - – New guidelines
  - » Requirements TEP very similar to those of sCTMP
    - – Requirements specific to Medical device component
    - – Interaction between cells and structural components

Procedure for revision (2)

- **Commission prepared a first draft Commission on basis of the EMEA technical contribution**
- **Public consultation (between April-June ’08)**
- **Review by EMEA of the contributions received**
  - » 44 contributions
  - » Patients, academia, industry, regulators, others
- **Amended EMEA technical contribution to EC**
- **Standing Committee**
  - » Adopted on 2 March 2009
- **Scrutiny period by European Parliament & Council**
- **Adoption by Commission & Publication in OJ**

News and Media
- Latest news on Pharmaceuticals
- News archives
- Speeches and Slide shows

3/30/09

02/04/2009 **Commission Directive regarding advanced therapy medicinal products approved by Standing Committee**
On 2 March 2009, the Member States have approved the new Commission Directive amending, as regards advanced therapy medicinal products, Annex I to Directive 2001/83/EC. The draft Directive was put to vote at a meeting of the Standing Committee on Medicinal Products for Human Use.
The text now enters a 3-months period of scrutiny by the European Parliament and Council, before it can be formally adopted by the Commission and enters into force.

The text of the draft Directive which was voted on 2 March 2009 is available here.

02/04/2009 **Draft Commission Regulation laying down provisions for the certification of quality and non clinical data for small and medium-sized companies approved by Standing Committee**
On 2 March 2009, the Member States have approved the new Commission Regulation laying down provisions for the certification of quality and non clinical data for small and medium-sized companies.
The draft Regulation was put to vote at a meeting of the Standing Committee on Medicinal Products for Human Use.
The text now enters a 1-month period of consideration by the European Parliament, before it can be formally adopted by the Commission and enters into force.

The text of the draft Regulation which was voted on 2 March 2009 is available here.

30/03/2009 **65th Pharmaceutical Committee – Meeting Report**
The 65th meeting of the Pharmaceutical Committee took place on 16 March 2009 in Brussels.

20/03/2009 **Implementation of the Variations Regulation**
Public Consultation Paper for the preparation of guidelines on the operation of the variation procedures
Article 4(1)(b) of Commission Regulation (EC) No 1234/2008 of 24 of November 2008 concerning

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new_en.htm

preparation of the Commission guidelines. It can be found here.

Annex I

- **Important to remember that Part IV of Annex I should be read together with the Part I of the Annex.**
  - » Not all requirements listed in Part I are repeated
  - » Part IV requirements explain how the technical requirements in Part I apply to ATMPs
  - » Additional requirements are identified based on the specificities of ATMPs.

What's new in the Annex I

- **Risk based approach**
  - » May be applied to determine extent of Q/N-C and C data
  - » Risk factors include
    - – Origin of cells, ability to proliferate / differentiate
    - – Level of cell manipulation
    - – Nature of gene therapy product
    - – Extent of replication competence of viruses ….
  - » Non-clinical/clinical experience with other ATMP
  - » Risk analysis to be included in Module 2

What's new in the Annex I

- **New definitions of**
  - » Gene therapy medicinal product
    - – Biological Medicinal products (synthetic oligonucleotides are not GTMP)
    - – Exclusion of vaccines against infectious diseases
  - » Somatic Cell therapy medicinal product
    - – sCTMP definition based on the new definition of TEP
    - – Cross reference to the list of non-substantial manipulations in Annex I to ATMP Regulation

What's new in the Annex I – Module 3

- Description of traceability system
- Gene therapy medicinal products
  - Description of what is considered the finished product, active substance, starting materials
  - Specific requirements
    - Information on starting materials
    - Product containing micro-organism or virus
    - Process / product related impurities
    - Plasmids
    - Genetically modified cells
      - Cross ref to quality requirements as described for sCTMP/TEP

What's new in the Annex I – Module 3

- Somatic Cell therapy medicinal products – TEP
  - Starting material
    - E.g. summary info on donation, procurement & testing
    - E.g. description of testing of additional substances (scaffolds, matrices, biomaterials …)
  - Manufacturing process
  - Characterisation and control strategy
    - Cell population, impurities, biologically active molecules
    - What expect if 3-D structure
  - Excipients
    - Requirements of 'novel excipients'

What's new in the Annex I – Module 3

- ATMPs containing devices
  - Device as referred to in art 7 of ATMP Regulation
    - Not a med. Device (scaffolds, biomaterials, matrices)
    - Description of physical characteristics, performance
    - Description of interaction with genes, cells, tissues
  - Combined ATMP
    - Cellular/tissue part: info as above
    - Info on choice/intended function of MD/implantable MD
    - Evidence of conformity with essential requirements
    - Evidence of compliance with BSE/TSE requirements
    - If available: result assessment by Notified Body

What's new in the Annex I – Module 4

- Acknowlegment that the standard module 4 requirements may not be appropriate to ATMP
- In the overview:
  - Rationale for non-Clinical development
  - Choice of relevant animal species and models
- Safety, suitability and biocompatibility of all structural componetns and additional substances

What's new in the Annex I – Module 4

- GTMP
  - Pharmacology: proof on concept; target selectivity
  - Pharmacokinetics: biodistribution, shedding
  - Toxicology:
    - Clarification of expectations for single/repeated dose, genotox, carcinogenicity, reprotox
    - Additional: integration studies, immunogenicity / immunotoxicity

What's new in the Annex I – Module 4

- CTMP / TEP
  - Pharmacology: proof concept, dosing, sec. pharmacology
  - Pharmacokinetics: viability, longevity, distribution, growth, distribution
  - Toxicity:
    - clarification of expectations
    - Products containing animal cell: transmission of xenogeneic pathogens

What's new in the Annex I – Module 5

- Need to study the therapeutic procedure as a whole
  - Surgery, comcomitant therapy
- Need to dose finding studies
- Clinically meaningful endpoints
  - For certain conditions: evidence of long term efficacy
- Stategy for long term S & E follow-up in the RMP
- For combined ATMP: clinical studies on the combined product

What's new in the Annex I – Module 5

- GTMP
  - Pharmacokinetic studies:
    - Shedding studies, biodistribution
    - PK on GTMP and on gene expression moieties
  - Pharmacodynamic studies:
    - Expression and function of nucleic acid sequence
  - Safety studies to address:
    - Emergence of Replication competent viruses
    - Emergence of new strains
    - Reassortment of existing genomic sequences
    - Neoplastic proliferation (due to insertional mutagenicity)

What's new in the Annex I – Module 5

- Somatic CTMP
  - If action is based on production of defined active biomolecules: PK profile to be addressed
  - Biodistribution, persistence, long term engraftment
  - Safety studies:
    - Distribution and engraftment
    - Ectopic engraftment
    - Oncogenic transformation / cell-tissue lineage fidelity
- TEP
  - PK: biodistribution, persistence, degradation

In conclusion

- **Annex I (Part IV) has been updated**
  - » Agreed version on DG Enterprise website

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new_en.htm

  - » Expected to become into force: July 2009

- **What's new**
  - » Risk based approach
  - » Definitions GTMP / somatic CTMP
  - » Dossier requirements for TEP similar to CTMP
    - – Especially for Module 3 and 4
  - » Additional requirements for combined ATMP

Thank you for your attention

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