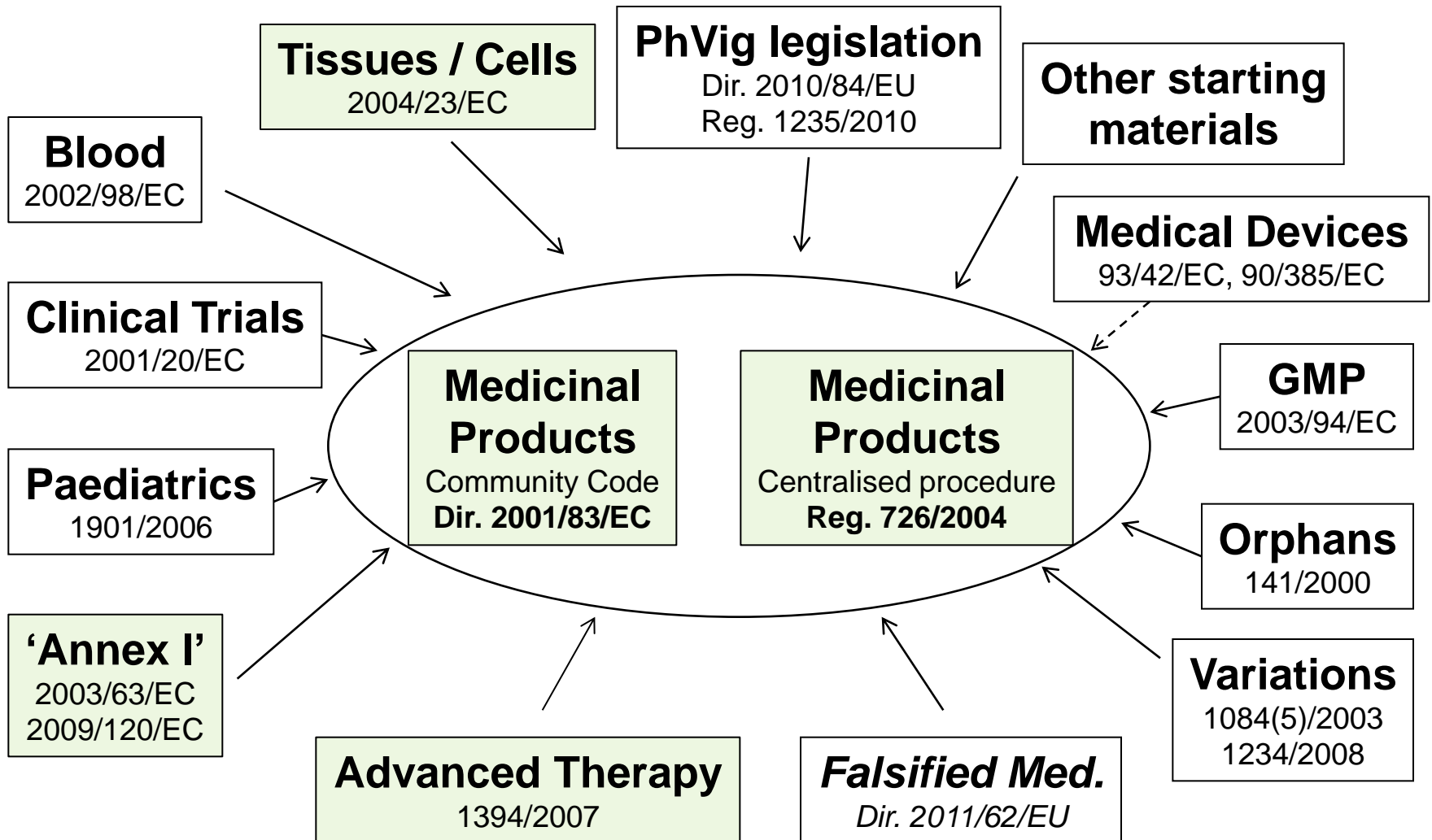


Clinical Exemptions from Marketing Authorisation

GRP Workshop
Auckland, New Zealand 22.4.2013



Products legally on national markets
via GMP certificate

Reg. 1394/2007/EC

Hospital exemption
Article 28, 1394/2007/EC

Transitional period
ATMPs, other than TEP 30.12.2011
Tissue engineered products, 30.12.2012

Marketing stopped

Centralised MAA

Authorisation of CBMPs outside centralised MA

- **Products nationally authorised under “hospital exemption” (art.28, Reg.1394/2007/EC)**
- **“Named patient” use (art.5 Dir.2001/83/EC)**
- **Compassionate use (art. 83 Reg. 726/2004/EC)**
- **Clinical trials (under remit of NCAs, Dir. 2001/20/EC)**

Article 28, 1394/2007/EC:

- Any ATMP, ..., which is prepared
 - on a **non-routine basis**
 - according to specific quality standards, and
 - used within the same Member State
 - in a hospital
 - under the exclusive professional responsibility of a medical practitioner
- in order to comply with an individual medical prescription for a custom-made product for an individual patient
- Manufacturing to be authorised by the MS competent authorities
- National traceability and pharmacovigilance requirements
- Specific quality standards ... as on the community level
- Currently under Commission evaluation (consultation and report)

National, non-industrial manufacturing of ATPs requires (National Regulation 3/2009)

- authorisation with inspection (Fimea)
- pharmacovigilance follow-up
- traceability follow-up
- compliance with the quality requirements (same level as for first in man clinical studies)

3.1.1 Product-specific quality requirements

The product-specific quality requirements must contain the following declarations:

- ✓ Declaration of the product's compliance with the principles of good manufacturing practice (**GMP**)
- ✓ Declaration of the product's **pharmacochemical and biological characteristics**. The guidelines of the Commission of the European Communities and the European Medicines Agency (EMA/CHMP) and the requirements of the European Pharmacopoeia must be observed when drawing up the declaration. The product must be characterised so as to make it possible to evaluate its **composition, identity and purity**.

The quality documentation must, in minimum, provide the following information:

- ✓ **Risk assessment** pertaining to the product based on known risk factors (such as infections, immunogenicity, tumorigenicity, loss of cell functionality, viruses contained in the gene therapy product capable of replication, retro-/lentiviral genome integration)
- ✓ Testing results for **starting materials** or the manufacturer's analysis certificate
- ✓ Testing of donors
- ✓ Suitability of materials (in particular the viral and TSE safety of materials of animal origin)
- ✓ **Compatibility** of non-cell-based components of combination products with cells and related testing (matrices, growth factors)
- ✓ Description of the **production process and validation of the aseptic process**
- ✓ **Key process controls** (microbiological control, cell growth control)
- ✓ Sufficient **characterisation** tests

The quality requirements (specifications) for the active ingredient and end product must always be presented accompanied by **analysis results for one or several lots**. The tests on the active ingredient and end product must address at least the following quality parameters:

- Identity test
- Microbiological purity / sterility
- Toxic / detrimental impurities
- Dose determination and testing
- Cell viability
- Evaluation of the tumorigenicity of stem cells and other cells grown for an extended period of time
- Gene therapy products: viruses capable of replication and the percentage of infective viruses of the entire virus population

- An adequate description is to be provided of all **analytical methods** used in product testing, and the main analytical methods must be qualified/validated
- If the product is stored before administration to the patient, research findings on the **shelf life** of the product in the proposed storage conditions must be provided
- Advanced therapy medicinal products must be packaged in compliance with the principles of good manufacturing practice for medicinal products
- Packaging must be labelled in compliance with the requirements presented in Annex 111 to the Regulation (EC) No 1394/2007 of the European Parliament and of the Council.

5.1 Tissue and blood safety

- In the event that human tissue or cells are used in the preparation of advanced therapy medicinal products, the recording and processing of adverse incidents and reactions related to the quality and safety of the products and the reporting procedures for serious adverse incidents and reactions must satisfy the provisions of Act on the Medical Use of Human Organs and Tissues and the more detailed regulations issued under said Act.
- In the event that human blood or its components are used in the preparation of advanced therapy medicinal products, the recording and processing of adverse incidents and reactions related to the quality and safety of the products and the reporting procedures for serious adverse incidents and reactions must satisfy the provisions of the Blood Service Act and the more detailed regulations issued under said Act.

5.2 Pharmacovigilance and annual safety reviews

- **Pharmacovigilance** of advanced therapy medicinal products must conform to the procedures set forth in the Medicines Act and the more detailed regulations issued under said Act.
- The manufacturer of the medicine is required to file with the Finnish Medicines Agency **an annual safety review** report concerning the advanced therapy medicinal products intended for the treatment of individual patients. The report is to be filed with the Finnish Medicines Agency by the end of March of the year following the year of manufacture. **The report must provide the data identifying the medicine, the production volume, the number of patients treated with the preparation, the name of the physician prescribing the medicine and responsible for care, as well as any serious adverse incidents in the preparation of the medicine or any adverse reactions caused by it.**