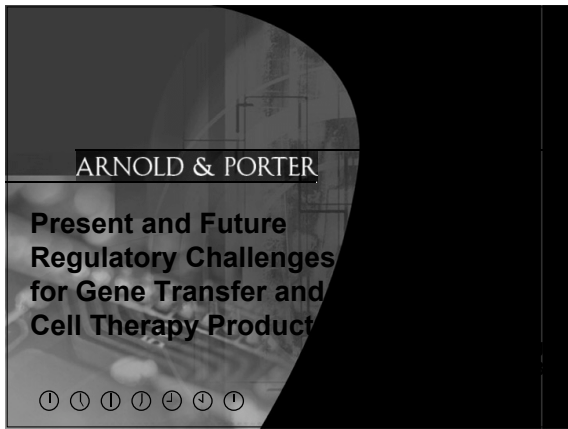
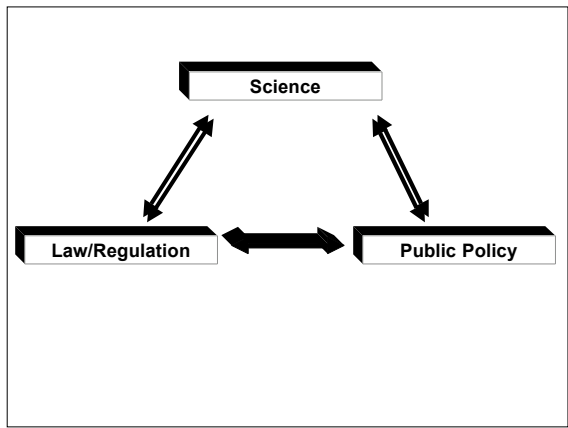


Session IV

The Regulatory Issues

11:50-15:15





- Regulatory Framework Objectives**
- Complete single market
 - Access to life-saving medicines in a timely manner
 - Public Health Protection
 - Articles 95(3) and 174(2)
 - Community policy on environmental protection
 - To achieve high level of protection concerning health, safety, environmental protection and consumer protection
 - Containment and Deliberate Release Directives
 - Article 152(4)
 - High level of human health protection
 - Closer co-operation in the sphere of public health
 - Measures to set high standards of quality and safety
 - Proposal for setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells

Regulatory Framework (cont'd)

- Evidence based: Risk/Benefit
- Mechanism based: To answer a series of questions
 - Why is this product safe and effective and what is the underlying mechanism?
 - What are safety features?
 - Biological plausibility
- What is the regulatory strategy to manage scientific uncertainties and risks arising from or in connection with (*combination products*) products derived from emerging technology?
- Evolution of medical practice is dynamic, learning and reviewing will unfold new scientific ideas that ultimately bring about clinically useful products.
- It is however important to formulate the best practice to minimise risk and ensure patient safety.
- To develop enabling provisions to allow the science to evolve

A failure to carry out a *thorough reappraisal* of the [development] programme and halt it until the methods of production were proved to be safe was negligent... *failure to lay down criteria*... assess the evidence and apply *standards and knowledge current* in the periods... to be *reasonably expected* of the doctors, scientists and administrators running the programme...

Many advances in medicine carry with them risks. A risk may be from a scientific point of view theoretical and may never become a reality. A risk may be real risk but weighed against the benefit of the drug or treatment...

But the *risks [relating to process]* of a drug or a treatment need *constant review* in the light of *expanding knowledge and experience*...

Growth Hormone Case 1996

- **Selectivity**
 - Transductional Targeting
 - Positional Targeting
 - Transcriptional Targeting
- Improved and new vectors
- Improved delivery systems
- Quality and process control and standardisation protocol for comparison of data set
- Safety Monitoring

**Genetically Modified Organisms
Environmental Risk Assessment**

- **Deliberate Release Directive already transposed into national law**
- **GMO organisms will be subject to standard authorisation and notification procedures prior to placing on the market or research and development**
- **Consent given by the Competent Authority is based on risk assessment based on identification and characterisation of hazard, and to appraise the risk as a result of exposure to GMO in order to determine the level risks. (Article 6(1))**
 - BUT sanction is subject to national rules but should be effective, proportionate and dissuasive
- **Current proposal for a new Directive on Environmental Liability to prevent and/or remedy environmental damage based on “polluter pays” principle (Treaty 174(2))**

Guiding Principles for Cell-based Products

- **Product safety**
- **Quality systems and standards in the sourcing, retrieval of tissues/cells, testing, processing, storage and delivery**
 - Microbiological and virological purity
 - Control and definition of the cell culture procedures
 - Characterisation of the cells
 - Specification and control of the final cell therapy product
 - Batch definition (what is a batch?)
 - Lot release testing and quality control
- **Post-marketing surveillance**
- **Consent**
- **Personal Data protection and confidentiality**
 - EU/US Safe Harbour Agreement (FTC clearance)

Stem Cell and Therapeutic Cloning

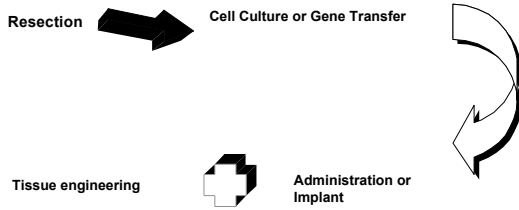
Potential to replace damaged body tissues

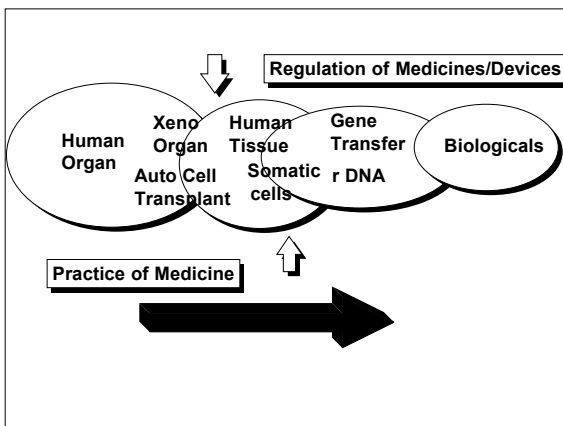
- **Evidence to establish plasticity of stem cells**
- **To establish a quality control system to form the basis of defining a product suitable for clinical trials in humans**
 - Need to build an inventory of genomic and phenotypic markers associated with different stages in the maturation of specific cell lineages
 - Optimisation of induction/cultivation procedure to elicit the desired cell differentiation
 - Uncharacterised cells other than enriched desired precursor cells
 - Cell proliferation capacity and control

Medicinal Products vs Medical Devices

- | | |
|--|--|
| <ul style="list-style-type: none"> • Physiological • Biological properties • Presentation • Claim • CPMP/Commission guidance • Constrained by 2001/83/EC | <ul style="list-style-type: none"> • Mechanical and physical • Presentation • Claim • 93/42/EEC • CE marking based on assessment of essential requirements (I, IIa, IIb, III) • Classification based on the level risk • Viable cells and human tissues excluded • 2000/70/EC (stable blood derivatives) • Commission Guidance (Meddev) |
|--|--|

Autologous and Allogeneic Cell Based Therapeutics





- **EU Framework Biotechnology Medicinal Products**
 - Medicinal product based (C98/C 229/03)
 - Mode of manufacture
 - Definition in terms of quantitative particulars of the active substances
 - Proposed revision of Annex I to Consolidated Directive includes the definition of a “*biological medicinal product*” and an “*advanced therapy medicinal product*”
 - Proposed Directive on the procurement, storage of tissue and cell
- **US §351 PHS, defines**
 - any virus, therapeutic serum, toxin, antitoxin, vaccine, blood and blood component or derivative allergenic product or analogous product
 - Safety, purity, potency of biologicals
 - Tissues and cells are regulated by FDA under the authority §361 PHS to prevent the introduction, transmission or spread of communicable diseases (delegated authority from Surgeon General and Sec HHS)
- **Japanese Proposed Regulation**
 - Products including ingredients derived from human or biological (excluding plants) source materials (such as cell, tissue, blood, etc.) , which should be subject to particular cares from public health point of view
 - Broader in scope to enable the Ministry to regulate new therapeutics

Novel Technologies

- **Regulation**
 - Framework
 - Quality Control and Standardisation (methodology)
- **Risk Assessment and Management**
- **Risk Communication**
- **Minimising liability exposure**
 - Contractual Liability
 - Product Liability
- **Bioethical issues including consent**

Needs for the Industry in Standardisation and Quality Control in the Framework of the European Regulatory Context

Dr. Erik Tambuyzer, Genzyme
Chairman EuropaBio Health Care Board



Cell and Gene therapy: long term strategy and investment needed

DON'T THINK WE'RE GOING
TO FEED YOU WHILE YOU
MESS ABOUT WITH
THAT!



February 2003

F. 003.006

Amali

EU regulations for Gene Therapy products: they are medicines (MPs)

- ◆ "Gene therapy is a set of processes aimed at the transfer of a gene to human tissues and its expression in vivo. The vectors have to be considered as part of the "product intended for gene therapy" which is a medicinal product in the meaning of the Community pharmaceutical legislation. (Commission communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03).)

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Current EU regulation for cell & tissue-based products

- ◆ No European wide regulation
 - Many products do not fit regulatory definition of medical devices or medicinal products
 - Member States legislation applies, if existing
- ◆ Resulting in
 - Unclear situation for future products/investments
 - Insufficient control on safety/efficacy
 - Trade barriers for industry
 - Equal access to European patients not ensured
 - EU member states introduce or review own legislation

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P. 4/18

Biotech medicinal products: 1. Regulations for placing on the market

- ◆ MP's require marketing authorisation, in principle only when "industrially produced", but likely to be interpreted broadly
- ◆ Review under the centralised procedure (2309/93)
- ◆ Scientific review by CPMP, upon positive recommendation of CPMP, decision by the Commission; includes environmental safety assessment
- ◆ For gene therapy MP's, no approvals yet, although many approvals exist for GMO derived products (e.g. recombinant proteins), some for veterinary products containing GMO's, (e.g. Suvaxyn Aujeszky 783+O/W viral vaccine, for pig vaccination)

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1. Placing on the market (continued)

- ◆ Standards for approval are being reviewed: draft new Annex I to Directive 2001/83 ("Human Use Directive"): deals primarily with requirements for protocols & testing of MP's; includes specific requirements for gene and cell therapy medicinal products
- ◆ Importance of definitions: somatic cell therapy medicinal products shall mean the "use in humans of autologous, allogeneic or xenogeneic somatic living cells, the biological characteristics of which have been altered to obtain a therapeutic effect through metabolic, pharmacological and immunological means"
- ◆ Being reviewed by Commission experts - to be approved by the pharmaceutical standing committee, expected in next months
- ◆ CPMP guidelines being prepared - gene therapy Expert Group established

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2. Regulations for medicinal products: Clinical trials

- ◆ Importance for gene and cell therapy products:
 - pre-clinical testing may be different; non-conventional clinical trials may be appropriate
 - emphasis *i.a.* on cell proliferation, risk of infection, impact on immune system, ...
 - specialised trial facilities required
- ◆ Currently clinical trials are still nationally regulated, e.g. :
 - suspension in Germany (by *Paul-Ehrlich-Institut* and *Bundesärztekammer*) of all retroviral gene transfer trials following adverse event in French INSERM / Hôpital Necker - Enfants Malades trial in Paris (June 2002)
 - UK Gene Therapy Advisory Committee guidance
- ◆ EU Clinical Trials Directive 2001/21: will be applicable at the latest as from May 2004
 - member states need to adopt and publish before (5/1/2003): "to simplify and harmonize provisions governing clinical trials"
 - review by national authorities competent bodies where clinical trials are intended + information to EMEA

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2. Clinical trials (continued).

- independent ethics committee review in the MS; for gene and cell therapy products: opinion = 90 days extendable for another 90 (xeno not time limit)
- require explicit written approval in case of gene & cell therapy
- "No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity" (art. 9.6)
- stricter national rules possible provided they are "consistent with the procedures and time-scales" under the directive (art. 3.1) – meaning unclear until implementation
- environmental assessment under GMO rules 90/219 (contained use) and 90/220 (deliberate use) still separate (Note : a patient is not a GMO in somatic gene therapy!)
- creation of a European data base only accessible by authorities
- mandatory liability coverage
- safety measures; notification of adverse events
- manufacturing under GMPs
- ◆ Question: will clinical trials for non-MP cell therapy products fit in, or will separate rules be created?

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Additional EU regulatory initiatives for cell therapy products in preparation

- ① DG Enterprise, MD Unit
 - Proposal for a Directive on human tissue engineered products which are not medicines and do fall outside the scope of the DG Sanco Directive in preparation
- ② DG Sanco (Health & Consumer Protection DG)
 - Proposal for a Directive on "Setting standards of safety and quality for the donation, procurement, testing, processing, storage and distribution of human tissues and cells" currently in the EP review process

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P. 9/18

DG Enterprise's proposal for Tissue Engineered products: what it may be?

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P. 1018

DG Enterprise Directive: history & timings

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P. 1118

- ◆ July 02: Public Consultation on the need for and content of a Community legal framework on Human Tissue Engineered Products
 - November 02 publication of results:
 - approx. 70 replies from governmental/national organisations, industry & individual experts
 - majority agrees on need for a new legislation
 - no consensus yet on definition of products/borderline or approval procedures
- ◆ April-May 03: public hearing/discussion with all parties
 - Current discussions seem to favour role for central expert committee, probably within EMEA, but with approval procedure based on Mutual Recognition
- ◆ June 03: draft proposal Directive expected

DG Enterprise Directive on tissue engineered products : key requirements for EuropaBio

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P. 1218

- ◆ Creation of new EU regulation specific for cell/tissue engineered products, outside MD & MP regulation, with categories based on
 - degree of manipulation
 - primary mode of action
 - having pharmacological, metabolic or immunological effect, as well as physiological/systemic effect
- ◆ Level playing field for all players, i.e. same regulations for all producers
- ◆ Specific and harmonised high quality, safety and efficacy European standards
- ◆ Data protection system because of difficult IP protection for innovation
- ◆ Centralised approval system, not mutual recognition, for clarity and legal certainty
- ◆ Central expert advisory body for tissue engineered products highly advisable, because of special expertise needed

DG Sanco proposed Directive: what is it ?

SOURCING

Donation, procurement, testing of tissues & cells of human origin and for the application in the human body

→ including starting materials for tissue and cell derived manufactured products
→ excluding autologous cells used for medicinal products

PROCESSING

Tissues & cells for transplantation
DG Sanco Directive

Tissues Engineered Products
DG Enterprise New Directive?

Cell-based Medicinal Products

Directive 2001/83/EC

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P. 13/18

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DG Sanco Directive: history & timings

- ◆ Need for European regulation defined during meeting under Portuguese Presidency, Porto June 2000
- ◆ Stakeholders meeting, Luxemburg December 2001
- ◆ Regulation idea reinforced under Spanish Presidency, Malaga February 2002
- ◆ Directive proposal on agenda of Health Council of Ministers, June 2002
- ◆ Health Working Party of Council July & September 2002
- ◆ Open debate Council 2 December 2002
- ◆ EP Public Hearing 29 January 2003
- ◆ EP Committee meetings & Report February & March 2003
- ◆ Plenary April May 03 - Second reading & vote end 2003
- ◆ Directive needs implementation by each of the member States, likely by 2005

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P. 14/18

EuropaBio's proposals related to the DG Sanco Directive

- ◆ Exclude both autologous and allogeneic cells used in industrially manufactured products for medical use from Directive
- ◆ Allow the accreditation of industrial manufacturers as a Tissue Bank
- ◆ Remove the testing of tissues and cells as tissue bank's responsibility
- ◆ Contracted third parties, non tissue banks, should be allowed to distribute human tissues and cells
- ◆ Delete the requirement of tissue banks to operate on a 24 hour basis
 - Tissue bank is responsible for processing, storage, and distribution (Article 3) but not for procurement and therefore no necessity is given to work on a 24 hour basis
 - Further, accredited tissue bank (industry working in production of tissue engineered products) and current tissue bank (working on storage of organs for transplantation purposes where urgency is given) activities should be differentiated
- ◆ Differentiate the requested laboratory tests between donors for autologous and for allogeneic cells

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P. 15/18

The issue of unregulated uses in the field of cell and gene therapy products

- ◆ Named patient treatment or hospital pharmacy preparations
- ◆ Subject to national professional rules
- ◆ National environmental GMO rules remain applicable

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P. 16/18

Conclusions

- ◆ Challenges
 - Consensus regarding ethical issues
 - Non-profit requirements
 - Definitions
 - IP/data protection
 - Reimbursement
 - Harmonisation of Member States regulation

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P. 17/18

Conclusions (continued)

- ◆ Need for consistency between the Commission's documents
 - DG Sanco Directive
 - DG Enterprise planned Directive
 - Annex 1 of 2001/83 for medicinal products
- ◆ Industry needs level playing field
- ◆ Industry is the source of innovative products and services, which European Citizens need: do we want to just import them?
- ◆ Harmonized European - or even global - regulations enable small & medium-sized companies to invest in development of cell & tissue engineered products: fit with EU Biotech strategic plan

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P. 18/18

Cell and Gene Therapy Products

Need for the industry in Standardisation and Quality Control

Strasbourg, 25 February 2003

Dr Christine-Lise Julou



Industry needs

- A clear legal framework
- A regulatory environment that is capable of evolving
 - as the technology, methods and models evolve
 - as new data become available
- A regulatory environment that supports clinical research and high quality drug development
- Regulators with a very strong scientific background and assessment experience and are given the opportunity to update their scientific knowledge.



A clear legal framework

- Legal framework
 - Need for safeguards when therapy products are administered to Human Beings
 - Need to know who is responsible for regulatory oversight (especially important when there are different bodies regulating different types of therapy products in a country)



A clear legal framework

- Legal framework needed to ensure the products meet obvious public health criterions
 - Therapeutic claims are substantiated
 - These therapeutic claims pertain to a well defined product
 - Possible risks to human health in particular, are appropriately assessed and do not outweigh (possible) benefits



A clear legal framework

- A legal framework accessible to all interested parties and that defines basic rights and obligations



Regulatory environment

Need for the responsible regulatory body to appoint staff with appropriate scientific education and assessment experience.



Regulatory environment

- Legally binding texts versus points to consider and notes for guidance documents
 - Texts that have been subject to « political » discussions (likely to be influenced by headline news at the time when they were discussed) vs texts based only scientific, technical and public health considerations
 - Texts that will be carved in stones and will not be easily modified vs texts that can evolve as the tools evolve and new experience is gained



Regulatory environment

- Some features of gene or cell therapies may be dealt with in laws initially written to address issues associated with other types of products, for example
 - Tissues and cells (technical and « ethical » considerations)
 - GMOs

Relevance of the provisions contained in these texts, ?



Regulatory environment

- Points to consider
 - Especially useful to draw attention on possible issues
 - Very useful means of communication because they are perceived as helpful/didactic tools and they can be amended easily



Regulatory environment

- Notes for guidance
 - Guide users on possible ways to address issues
 - Can evolve fairly easily .



Regulatory environment

- Notes for guidances, standards
 - can support quality development and thus help new products become available to patients
 - or they can freeze development and discourage innovation



Regulatory environment

- Supporting quality development or freezing development/discouraging innovation? (examples for gene therapy)
 - Facilitating the development of international standards
 - **Defining Criteria**s for determining acceptable levels of production impurities (or hastily setting rigid limits?)



Regulatory environment

- Supporting quality development (examples for gene therapy)
 - Product characterisation in relation to the phase of development
 - Scale-up, process improvements and vector improvement during the course of development and need for comparability studies, repetition of preclinical and clinical studies (impact on vector improvement strategies and production strategies)



Regulatory environment

- Good practices in Gene and Cell Therapy
 - Good Manufacturing Practices (general principles can apply but for practical reasons some « requirements » cannot apply and have to be adapted)
 - Good Laboratory Practices
 - Good Clinical Practices (ICH, WHO, versus European Directive 20/2001/EC)



Supporting Clinical Research

- Clear legal framework; legislation accessible to all; one door-one key
- Centers will be selected based on the following criterions:
 - Size/availability of target patient population and availability of high quality multidisciplinary teams with experience in clinical research
 - regulatory constraints-administrative burden/time necessary to obtain all necessary permissions/ experience of local reviewers/ possibility of dialogue/advice



Supporting Clinical Research

- Need for nonclinical research to work in close cooperation with production /quality control and with clinical research;



Supporting Cell and Gene Therapy

- Communicate on what really are gene and cell therapies;
- Define a clear, simple and light legal framework
- Promote cooperation and dialogue between all interested parties to be in a position to develop appropriate standards, guidelines and relevant regulatory requirements
- Encourage **all** teams to formalise protocols and generate quality/well documented data (the only data that will make it possible to draw relevant/useful conclusions to make gene and cell therapy progress)





Maurice Pierre ROBERT

European Commission
DG Enterprise - Pharmaceuticals Unit

Brussels



As to the European Community Law,

what is the legal status applicable to :

- Gene therapy products
- Cell therapy products ?



Gene therapy and cell therapy products are

- Medicinal Products in the sense of Article 1 of Directive 2001/83/EC ;
- This is confirmed by Directive 2001/20/EC on Clinical Trials on Medicinal Products for human use.



Article 1 to Directive 2001/83/EC

Medicinal product :

“Any substance or combination of substances:

- presented for **treating** or **preventing** disease in human beings,
- which may be administered to human beings with a view to making a medical **diagnosis** or to **restoring, correcting** or modifying physiological functions in human beings.”



Article 1 to Directive 98/79/EC

‘**medical device**’: any *instrument, apparatus, appliance, material* or other *article*, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of :

- diagnosis, prevention, monitoring, treatment or alleviation of disease, alleviation or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception, and

which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.



Annex I to Directive 2001/83/EC Part IV : Advanced Therapy Medicinal Products

Gene therapy medicinal product : “ a set of manufacturing processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression *in vivo*. The gene transfer involves an **expression system** contained in a **delivery system** known as a **vector**, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.”



Annex I of Directive 2001/83/EC
Part IV : Advanced Therapy Medicinal Products

Somatic cell therapy medicinal product : “ the use in humans of **autologous** (from the patient himself), **allogeneic** (from an other human being) or **xenogeneic** (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 and activation of autologous cell population *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-degradables or not).”



Commission Communication 98/C 229/3

A. SCOPE OF APPLICATION OF COUNCIL REGULATION (EEC) No 2309/93

- 1. Part A of the Annex - biotechnology-derived products**
 (a) Medicinal products developed by means of recombinant DNA technology
 (b) Products intended for Gene therapy
 (c) Cell therapy

2. Part B of the Annex - high technology products and products containing new active substance

- (a) Conditions of implementation of Article 10 of Directive 2001/83/EC
- abridged applications “informed consent”
 - “generic application”
 - bibliographical applications

(b) Medicinal products containing the same active substance(s) as a Community authorised products

B. INTRODUCTION OF A BIOTECHNOLOGY MANUFACTURING STEP AFTER THE GRANTING OF A MARKETING AUTHORISATION

- 1. The constituents concerned by the introduction of recombinant technology is of a proteinaceous nature**
2. Other cases



Recital (7) of Directive 2001/20/EC on clinical trials

“ For medicinal products falling within the scope of **Part A** of the Annex to Council Regulation (EEC) No 2309/93 [...], which include products intended for gene therapy or cell therapy, prior scientific evaluation by the EMEA, assisted by the CPMP, is mandatory before the Commission grants marketing authorisation. [...].

Provision must therefore be made to allow the Agency to have full information on the conduct of any clinical trial for such medicinal products.”



Article 9 of Directive 2001/20/EC

5. Without prejudice to paragraph 6, written authorisation may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing authorisation within the meaning of Directive 65/65/EEC and are referred to in Part A of the Annex to Regulation (EEC) No 2309/93...
6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.



Gene Therapy Medicinal Products

- 1 – **Allogeneic + xenogeneic hosting cells :**
vector = ready-prepared + stored
“active substance” = cells genetically modified by the vector
“medicinal product” = administered several patients
- 2 – **Autologous hosting cells :**
“active substance” = ready-prepared vector
“medicinal product” = administered to the cell donor
- 3 – **In vivo :**
“active substance” = ready-prepared vector



Gene Therapy Medicinal Products

Module 3 : specific requirements

- relevant characteristics = expression in the target cell population; encoding therapeutic gene sequence; other genes
- characterisation of the vector = physico-chemical + biological/immunological; biological gene transfer
- cell banking for seed lot establishment
- source of hosting cells
- viral safety + traceability of products from donor to finished medicinal product .



Somatic cell therapy medicinal product

- cells manipulated to modify their immunological, metabolic or other qualitative or quantitative aspects
- cells sorted and manipulated + manufacturing process
- cells manipulated and combined with non-cellular components
- autologous cell derivatives expressed *in vitro*
- cells genetically modified or otherwise manipulated to express previously unexpressed homologous or non-homologous functional properties.



Proposed Directive on Human Cells and Tissues as Starting Materials

OJ 2002/C 227 E/28 ; 24/09/02

- **Standards of Quality and Safety for**
- donation, procurement, testing of human tissues & cells
→ application to the human body
- processing, storage, preservation and distribution of human tissues and cells → human transplantation
- **Autologous cells to be used for the manufacturing medicinal products are excluded .**



ANNEX I to DIRECTIVE 2001/83/EC

Part IV Advanced therapy medicinal products

- Gene therapy medicinal products using autologous human cells
- Cell therapy medicinal products

The whole manufacturing process from the collection of the cells from the patient (autologous situation) up to the re - injection to the patient shall be considered as one intervention .



DIFFERENT TYPES of HUMAN

CELLS for

– Transplantation

Not regarded as products

– Somatic cell therapy

Regarded as products

– Difference between cell therapy *versus* transplantation

- extent + intent of the cell processing, or
- way in which the biological characteristics of the cells have been altered .



Proposed Directive

OJ 2002/C 227 E/28

- Human **autologous** tissues & cells
 - transplantation = **YES**
 - medicinal product = **NO**
- Human **allogenic** tissues & cells
 - transplantation = **YES**
 - medicinal product = **YES**

Cell & Gene Therapy Products The French Experience

*EDQM, European Pharmacopeia
Strasbourg, 24-25 Feb. 2003*

*P. Zorzi
S. Lucas – F. d'Herbes*



CONTENT

- I - Legislative & Regulatory Framework
- II - Definition & Principles
- III - Clinical Trial Experience
- IV- Afssaps Procedures and Responsibilities
- V - Technical Requirements for Process/Product authorisation

2

I - Legislative & Regulatory Framework

Laws

GMO (92) - Bioéthique (94) - DMOSS (96) - "Afssaps"(98)



Afssaps : Authority Responsible for

- Cellular Ther. / Gene Ther.
- Ancillary products
- Tissues, Organs
- Biovigilance

3

Decree 1st Oct 2001

Authorisations

- Clinical trials (L.1125-1 / L.1125-4)
- Process / Products (L.1261-3 / L.1243-6)
 - Proprietary medicinal products
 - Non proprietary med products : ex vivo preparation
- Production/preparation sites
 - Private Cies : pharmaceutical establishments (but also non pharmaceutical)
 - Public organisms

4

Current Situation

- Clinical trial evaluation
 - Gene therapy : since 1993
 - Cell therapy : since 1996
- Finalisation of the regulatory framework
 - “Arrêtés ” to officialize various formats still pending
- European registration
 - proprietary medicinal products

5

II - Definition and Principles

- Cell Therapy Definition
Administration to a patient
 - of a cell preparation (autologous, allogeneic, xenogeneic)
 - presenting defined characteristics
 - to treat or to prevent human pathologies

6

Definition and Principles

- Gene Therapy Definition
Transfer of genetic material, by vectors administered *in vivo* or *ex vivo*, to obtain *in vivo*, in human tissues, the expression of the gene of interest, for therapeutic or diagnostic purposes

7

Two Situations

- Proprietary medicinal products
 - Recombinant viral vectors
 - Allogeneic fibroblasts (diabetic fore-foot ulcer)
- Non proprietary medicinal products
 - Autologous : Hematopoietic stem cell (cancer), Keratinocytes (burned patients)
 - Allogeneic : pancreatic cells (diabetes patients), fetal neurons (Parkinson, Huntington)

8

Production/Preparation Process

Three key steps

- 1 - Starting materials : materials from which the active substance is manufactured
 - *Gene therapy* : cell banks and virus seed lots (gene of interest, expression vector)
 - *Cell Therapy* : autologous, allogeneic, xenogeneic cells (from organ or tissues) or cell bank system (continuous cell lines)

9

Production/Preparation Process

Three key steps

2 -Bulk of active ingredient

- *Gene therapy* : rec. vectors, naked or complexed plasmids, virus producing cells, in vitro genetically modified cells (allog. xenog.)
- *Cell therapy* : pool of manipulated cells (whatever the complexity of the process), cell lysates, cells used in conjunction with inert matrixes and medical devices.

3 - Finished medicinal product

- Active ingredient formulated in its final immediate container for the intended medical use.

10

AGENCE
PRODUITS = SANTE

Different Situations

Pharma. Establishments
or non Pharma. Est.(public/private)

Proprietary
or
non Propr
Med. Prod.

Same manufacturing steps

- Starting materials
- Bulk active ingredient
- Finished medicinal product



Same requirements

- QA system
- Starting materials (quality/traceability)
- Process validated and reproducible
- QC of the product to be administered

11

AGENCE
PRODUITS = SANTE

Production/Preparation Process

• Simple Processes

- Autologous HSC frozen/ stored /shipped prior re-administration

• Complex Processes

- Cell therapy : selection, propagation, differentiation, incorporation into a matrix...
- Gene therapy i.e. viral vectors : banking system, culture, purification and lyophilisation

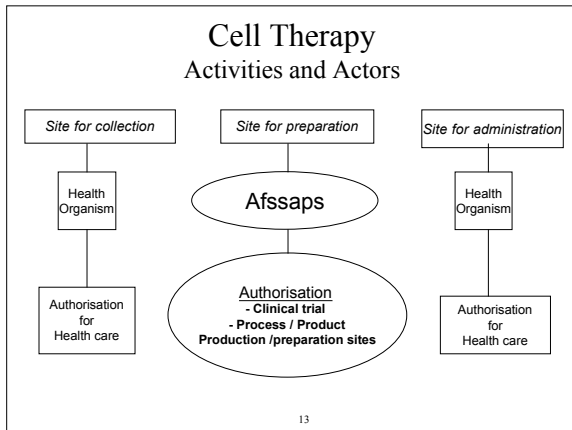


Three key steps (closely related for simple processes)

Process validated and reproducible

12

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PRODUITS = SANTE

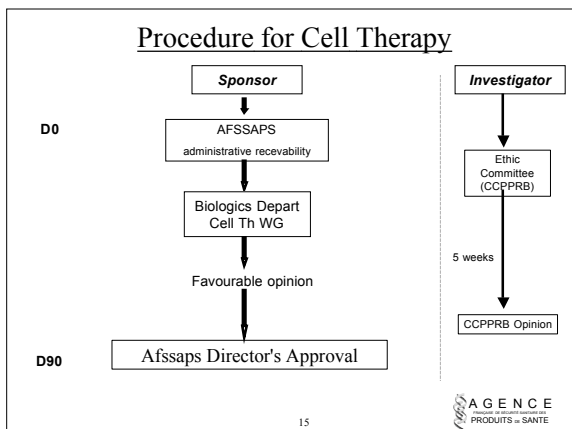


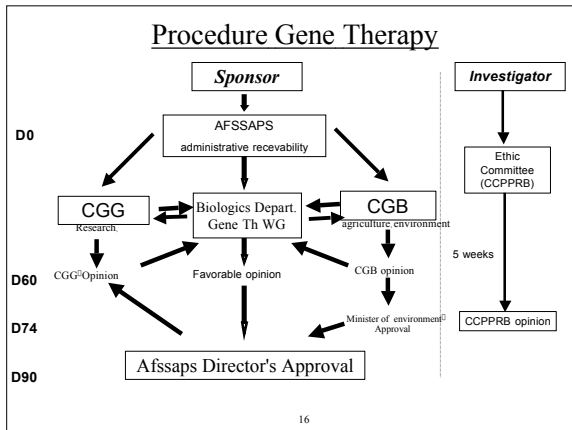
III - Clinical Trial Experience

- Dossiers submitted
 - Gene therapy since 1993 (GMO Law of 1992)
 - Cell therapy since 1996
- Procedure :
 - Afssaps authorisation
 - For Gene therapy, advice from CGG, CGB
 - Local ethical committee : favourable opinion
- European directive for clinical trials
 - Consistent with Afssaps procedures

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14






Clinical Trial Dossier

French format regularly updated

- (1) Pharmaceutical and biological information
 - Facilities and environment, equipment, personnel, QA system
 - Production/ Preparation process, controls
 - Quality of starting materials (cells, banks...),
 - Quality of other raw materials (biological origin...) and ancillary products,
 - Quality control of the product
 - Storage, shipment...
- (1*) Information on GMOs : containment and risk for deliberate release (for gene therapy)
- (2) Pharmaco-toxicology data (Scientific rationale)
- (3) Clinical trial protocol



17

Cell Therapy Clinical Trials Overview (1)

- since 1996 ~ 140 trials
- Sponsors
 - 80% from public organisations
 - Others from pharmaceutical industry (HSC associated to a drug under development, biotech company for the preparation of cell therapy products...)
- Type of cells
 - 60% HSC
 - 75% autologous



18

Cell Therapy Clinical Trials (1)

Activated macrophages / Dendritic cells	Melanoma, various cancers (kidney...)
Hematopoietic stem cells	- Hematology : malignant lymphoma, multiples lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) - Improvement of chemotherapy
Dendritic cells-derived dexosomes / Solubles antigens	Immunotherapy of advanced cancers : melanoma, lung cancer...

19

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Cell Therapy Clinical Trials (2)

Chondrocytes	Defects of articular cartilage in the knee
Human keratinocytes +/- fibroblasts	Chronic venous ulcers / diabetic fore- foot ulcer... Burns wounds Second and third-degree burns
Fetal dopaminergic neurons Fetal striatal neuroblasts	Parkinson's disease Huntington's disease
Myoblasts	Severe postinfarction left ventricular dysfunction
Pancreatic islets	Type I diabete (insulin - dependant)

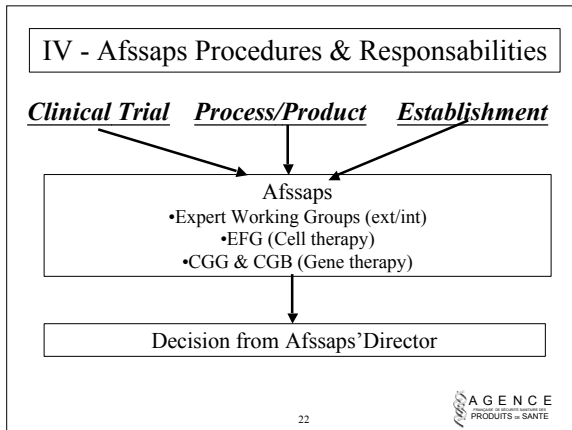
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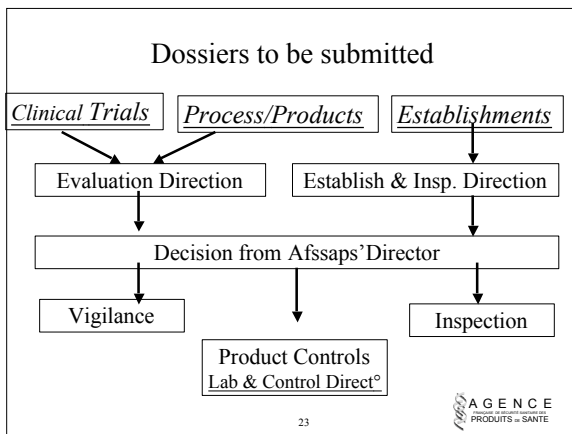
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Gene Therapy Clinical Trials Overview

Number 53	Industrial /34 Institutions /19	Strategy	In vivo / 43 Ex vivo / 10
Vect .Viral .nonV	Rétrov /14, Adeno/ 14, Others/11 (vaccinia, AAV...) Plasmids/14 (complexed or not)	Finished Product	Viral susp Virus produc. cells Plasmids Xenogenic cells
Gene of int	HSV-tk/12, IL-2/13 CFTR/3, LacZ/3, p53/3 FGF/VEGF/3 Others (PSA, Ada, GM-CFS, FVIII...)	Indication	Cancer/hemato / 39 Genetic diseases/ 8 Others (AIDS, vasc diseases...)

21





Vigilances

- Pharmacovigilance
 - Proprietary medicinal products
- Biovigilance

Surveillance of adverse effects possibly linked to organs, tissues, cells and ancillary products

24

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V - Technical Requirements for
Process/ Product Authorisation

Quality, Safety, Efficacy

- 1-Quality data
- 2-Non-clinical data
- 3- Clinical data

25

European Guidance Documents

- Cell Therapy
Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products (CPMP/BWP/4150/98)
- Gene Therapy
Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/5863/93)
- Xenogeneic
Points to consider on xenogeneic cell therapy medicinal products (CPMP/1199/02)

26

1- Quality Data

- Starting materials and other raw materials
- Manufacturing/Preparation process
- Quality control of the finished product
- Viral safety

27

Starting and Other Raw Materials

- Starting materials

- Gene therapy :

- Gene of interest, expression vector : source, construction, characterisation and controls including verification of its integrity and stability
 - Cell hosting the recombinant vector : source, characteristics
 - Cell banks/virus seed lots : preparation, controls, storage

- Cell therapy : Autologous, Allogeneic, Xenogeneic cells

- Donors : clinical and biological selection, collection condit.
 - Cell banks (xeno)
 - Controls : viability, identity and purity

28

Starting and Other Raw Materials

- Ancillary products (Art L.1263-1)

- Definition :

- product in contact with organs, tissues, cells, or embryos
 - used during processing, storage or shipment before therapeutic use in human
 - from chemical or biological (human or animal) origin

- Requirements : Afssaps Authorisation

- Quality : production process, quality of raw material, quality control
 - Safety/in vitro activity : biblio./experimental data

- Other raw materials

29

Production/Preparation Process

Whatever the type of process
(simple or complex)

- Name of the manufacturer
- Description and flow chart (from starting materials up to product to be administered)
- In-process controls : to ensure that the process is run in a consistent manner
- Identification of critical steps and intermediates : with appropriate controls
- Process validation : demonstration of consistency

30

3 - Clinical Data

- Clinical data supporting the therapeutic indication (experimental and/or bibliographic)
- Dosage, precautions, adverse events...

34

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Conclusion

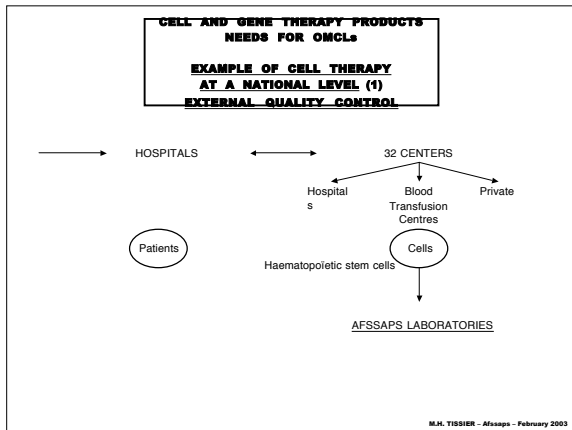
French regulatory framework in place

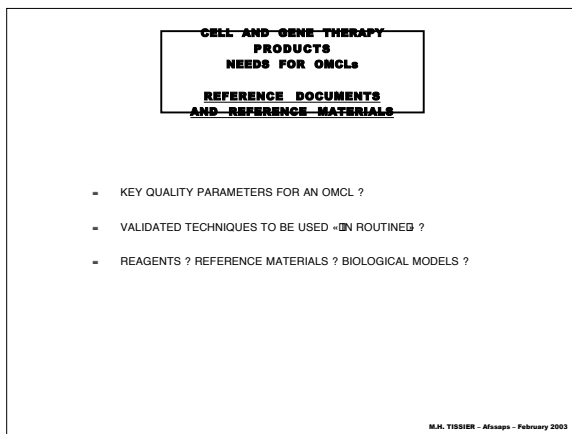
Authorisation for Process/product
Manufacturer authorized

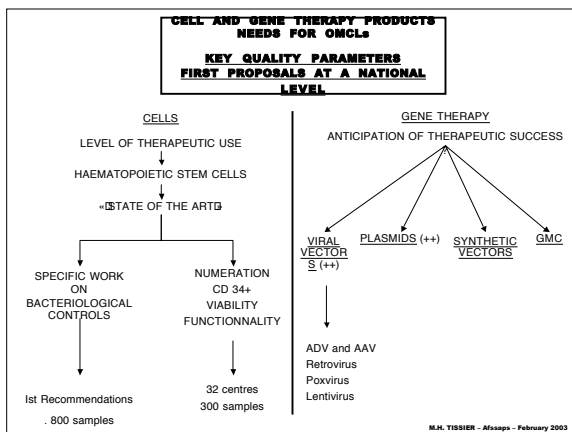
- to commercialize a product
- for a given therapeutic indication
- according to a define process
- performed in an authorized establishment

35

 A G E N C E
P R O D U I T S - S A N T E







**CELL AND GENE THERAPY PRODUCTS
NEEDS FOR OMCLs**
SAMPLES

IMPLEMENTATION OF «GOOD PRACTICES»

- WHO CAN PROVIDE «GMP» SAMPLES ?

- CELL BANKS ?
INVESTIGATOR OF CLINICAL TRIAL ?
PRODUCER ?
MANUFACTURERS ?

M.H. TISSIER - Afsaaps - February 2003

**CELL AND GENE THERAPY
PRODUCTS
NEEDS FOR OMCLs**
PREMISES

- HANDLING OF GENETICALLY MODIFIED PRODUCTS

- LEVEL OF SAFETY ?
 - NO PRODUCTION BY OMCLs
 - SAMPLES OF LOW TITERS ?IN ROUTINE : L2 IS SUFFICIENT
AVAILABILITY OF L3 FOR THE OMCL NETWORK

- ANIMAL HOUSING FACILITIES ?
ONLY TO CONDUCT SIMPLE TESTS ON SMALL RODENTS

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**CELL AND GENE THERAPY
PRODUCTS
NEEDS FOR OMCLs**
CONCLUSIONS (1)

- RECORDING OF OMCLs FACILITIES

- RECORDING OF PRODUCERS / MANUFACTURERS

- DEFINITION OF PRIORITIES

- INITIATION OF A COLLABORATIVE APPROACH WITH THE EUROPEAN PHARMACOPOEIA

DIFFICULTIES

- NO REGISTERED PRODUCT
- NO INDUSTRIAL LEVEL OF PRODUCTION

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**CELL AND GENE THERAPY
PRODUCTS
NEEDS FOR OMCLs**

CONCLUSIONS (2)

MONOGRAPHS

- Bacteriological control of haematopoietic stem cells
- General chapters already published completed (i.e. : mycoplasmae)
- Specific monographs for gene therapy vectors

COLLABORATIVE STUDIES

- Detection of mycoplasmae
- Titration of viral vectors
- Detection of RCV
- Preparation of titrated solutions of viral vectors

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**CELL AND GENE THERAPY
PRODUCTS
NEEDS FOR OMCLs**

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