CURRENT EUROPEAN REGULATORY FRAMEWORK FOR GENE THERAPY

ECL Annual Conference

State of the Art in Genetics, Genomics and Cancer

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Purificación TEJEDOR DEL REAL
Policy Department A
Directorate A: Economics and Scientific Policy
Directorate General for Internal Policies
European Parliament
The Treaty of Lisbon

The Treaty of Lisbon enhances the importance of health policy. In Title XIV, Public Health, Article 168 (ex-Article 152 TEC), it is stipulated that "a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities".

This objective is to be achieved through Community support to Member States and by fostering cooperation. Primary responsibility for health protection and, in particular, the healthcare systems themselves, remains at Member State level. However, the EU has an important role to play in improving public health, preventing and managing diseases, mitigating sources of danger to human health and harmonising health strategies between Member States.

Health Strategies:
"Together for Health" and its action program (2007-2013)
"Health for Growth" foreseen for the period (2014-2020)
EU Health Policy

The three strategic objectives:
Â Fostering good health
Â Protecting citizens from health threats
Â Supporting dynamic health systems

Institutional set-up to support implementation:
Â Directorate General for Health and Consumer Protection (DG SANCO)
Â European Medicines Agency (EMA)
Â European Centre for Disease Prevention and Control (ECDC)
Legal framework governing medicinal products for human use in the EU

The EU legal framework for medicinal products for human use intends to ensure a high level of public health protection and to promote the functioning of the internal market, encouraging innovation.

Main principle:
Marketing authorisation (Directive 2001/83/EC, Regulation (EC) No 726/2004) by the competent authorities to place on the market a medicinal products. A large body of legislation has been developed around this principal

Specific areas:
- Orphan medicinal products (Regulation (EC) No 141/2000)

All Community Legislation in: "The Rules Governing Medicinal Products in the European Union"
Advanced Therapy Medicinal Products

• Gene-therapy medicines: these contain genes that lead to a therapeutic effect.
• Somatic-cell therapy medicines: contain cells or tissues manipulated to change their biological characteristics.
• Tissue-engineered medicines: contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue.
• Combined advanced-therapy medicines: medicines that contain one or more medical devices as an integral part of the medicine.

This emerging field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body and enormous potential industry. However, some challenges exist.
Definition of Gene Therapy Medicinal Product


Gene therapy medicinal product means a biological medicinal product which has the following characteristics:
(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.
The Principle of Gene Therapy

The introduction of nucleic acids into cells to alter gene expression in order to prevent, halt or reverse a pathological process
- Gene addition: to replace an altered, non functional gene
- Gene correction/gene alteration
- Gene knockdown (RNA interference)

Vectors are in general derivatives of viruses where detrimental sequences are replaced by therapeutics sequences.

To be successful, actors in various domains must be involved:
- Medicine
- Virology
- Vectorology
- Biotechnology
Advanced Therapy Medicinal Products

The main elements of the Regulation:

- A centralised marketing authorisation procedure
- A new and multidisciplinary expert Committee (Committee for Advanced Therapies), within the European Medicines Agency (EMA)
- Technical requirements adapted to the particular characteristics of these products.
- Principles of quality, safety and efficacy apply
- Hospital exemption providing hospitals and Member States with an opportunity (under narrow conditions) to authorise an advanced therapy without going through the mandatory centralised procedure at the European level
- Special incentives for small and medium-sized enterprises
Committee for Advanced Therapies (CAT) - EMA

Composition:
- Five members or co-opted members of the Committee for Medicinal Products for Human Use (CHMP) with their alternates;
- One member and one alternate appointed by each European Union (EU) Member State;
- Two members and two alternates appointed by the European Commission to represent clinicians;
- Two members and two alternates appointed by the European Commission to represent patient associations.

The main responsibility: to prepare a draft opinion on each ATMP application submitted to the European Medicines Agency, before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorisation for the medicine concerned.
Directive 2009/120/EC

3.2 Specific requirements for gene therapy medicinal products

3.2.1. Introduction: finished product, active substance and starting materials

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.

3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

3.2.2. Specific requirements

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;

(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;

(c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality require
4.2. Other Specific requirements for gene therapy medicinal products

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1. Pharmacology

(a) In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic "proof of concept" studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. Pharmacokinetics

(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. Toxicology

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) Additional toxicity studies

δ 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 germline transmission.

δ Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.
5.2 Other Specific requirements for gene therapy medicinal products (clinical application)

5.2.1. Human pharmacokinetic studies
Human pharmacokinetic studies shall include the following aspects:
(a) shedding studies to address the excretion of the gene therapy medicinal products;
(b) biodistribution studies;
(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

5.2.2. Human pharmacodynamic studies
Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

5.2.3. Safety studies
Safety studies shall address the following aspects:
(a) emergence of replication competent vector;
(b) emergence of new strains;
(c) reassortment of existing genomic sequences;
(d) neoplastic proliferation due to insertional mutagenicity.
European Cancer Situation

- Cancer incidence in Europe is still increasing

- Access to appropriate health care for cancer differs significantly among member states

- Cancer is an important policy concern for public health in Europe; there is a considerable scope for action at the EU level, both in promoting research and in sharing the available knowledge.

- European cooperation can help to share knowledge and combine resources efficiently to tackle cancer and specifically rare cancer
Overview (1)

Cancer is caused by many factors and therefore its prevention shall address on equal footing the lifestyle, occupational and environmental causes:

- Tobacco Directive 2001/37/EC
- Pharmacovigilance Directive 2001/20/EC
This Regulation respects the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union and also takes into account the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.
Clinical trials

The European Clinical trials Directive (Directive 2001/20/EC) has the aim of simplifying and harmonising the administrative of clinical trial participants, the ethical soundness of trials and the reliability and robustness of data generated.

The system needs to be operational with multinational trial working in the benefit of the patients.
Overview (3)

Resolution of the European Parliament (10 April 2008) on combating cancer in the enlarged EU.

Conclusions of the Council (10 June 2008) on reducing the European burden of cancer.

Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, (2009) on European Partnership on Action Against Cancer: to support the Member State in their efforts to tackle cancer to be reduced by 15% in 2020. Actors at EU level, including Member States, experts, health care professionals, NGOs, patient groups, civil society representatives and industry, as a model for non-communicable diseases in general.
Overview (4)

Others:

- EU Platform for Action on Diet, Physical Activity and Health and the Alcohol and Health Forum

The MEPs Against Cancer (MAC) group

The MEPs Against Cancer (MAC) group is an all-party informal group of Members of the European Parliament (MEPs) at the European Parliament committed to promoting action on cancer as an EU priority and harnessing European health policy to that end. MAC will focus on prevention.

 MEP Alojz Peterle, MAC President
The committee called on both national and EU lawmakers to influence developments in biotechnology and medicine through the way in which funding was allocated. A harmonised regulatory framework at European level was needed.

The report also highlighted the thorny issue of the patentability of living human material, in connection with Directive 98/44/EC on the legal protection of biotechnological inventions. The committee argued that all living matter must be deemed to be non-patentable.

Rejected
Cancer Research

Mainly undertaken at national level, considerably fragmented and diverse across the EU

Cooperation and coordination:
6th FP & 7th FP have devoted about €750M to cancer research
- FP7 European network for cancer research in children

IMI (Innovative Medicine Initiative) is a pan-European public and private sector collaboration endeavouring to support the discovery and development of better medicines, including cancer therapies

ESFRI Roadmap (Infrastructures) includes projects to support the establishment of clinical trials and bio-banking facilities as well as cancer treatment to pave the way for a more harmonised European framework.
The International Bioethics Committee of Unesco (IBC) at the conclusion of its Eighth Session on 14 September 2001 which states ‘that there are strong ethical grounds for excluding the human genome from patentability’ and further recommends ‘that the World Trade Organisation (WTO), in its review of the TRIPS Agreement, clarify that, in accordance with the provision of Article 27(2)1, the human genome is not patentable on the basis of the public interest considerations set out therein, in particular, public order, morality and the protection of human life and health’.

The European Patent Convention, in particular its Article 52.2(a), stipulates that no patents shall be granted for discoveries, and Article 53(a) excludes inventions, the publication or exploitation of which would be contrary to ‘ordre public’ or morality from patentability.
Public Consultation

The EC launched a Public Consultation on the Regulation on Advanced Therapy Medicinal Products (20 December 2012) to explore views of interested parties (stakeholders including small and medium enterprises) in order to seek the view of stakeholders regarding the application of the Advanced Therapy Regulation.

Contributors included:

ÂAcademia: university hospitals and other entities involved in the research of innovative treatments

ÂHealth care sector: hospitals (other than university hospitals), blood, tissue and cells establishments

ÂIndustry: individual entities and associations of companies engaged in the development of ATMPs, medicines, or medical devices

ÂNon-for-profit organisations: patient associations and other non-for-profit associations

ÂPublic authorities: national medicines agencies and other public authorities
Outcome of the Public Consultation (1)

The ATMP Regulation was considered an important tool to improve the regulatory framework for advanced therapies in the EU by many contributors.

The high requirements of Regulation were however blamed for the disappearance of some innovative products from the market, which discouraged new developments.

The current requirements do not take into account the practical limitations faced by SMEs, which constitute the majority of the entities that are currently involved in research and development of ATMPs.

This prevents the majority of developments in this area from going beyond the "hospital exemption" or other derogations under national law, thereby creating a fragmented market in the EU.
Outcome of the Public Consultation (2)

- Marketing authorisation application requirements for advanced therapy medicinal products: request for additional flexibility & major changes in the authorisation system with the introduction of a stepwise. Specific GMP guidelines should be developed for ATMPs authorisation.

- Requirements for combined advanced therapy medicinal products: A single assessment of the combination product

- Hospital exemption: lack of a harmonised approach to the application of the exemption; scope is too broadly; critical tool for the development of new innovative therapies

- Specific GMP guidelines should be developed for ATMPs
Outcome of the Public Consultation (3)

- Incentives for the development of advanced therapy medicinal products: extension of incentives to academia and other non-for profit organisations

- Scope and adaptation to technical progress: the boundaries between the ATMP Regulation and other legal instruments, such as the Directive on Human Tissues and Cells,3 or the Clinical Trials Directive4 are not sufficiently clear. Need to ensure rapid adaptation of the law to the fast evolution of science

NEXT STEP
Commission Report on the application of the Advanced Therapy Regulation
Policy, research and industry has to focus on the right issues regarding treatment!!!
THANK YOU!!!