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ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
**Pharmaceuticals**

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# IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION

*Regulation (EC) No 1394/2007*

## AMENDMENTS TO ANNEX I TO DIRECTIVE 2001/83/EC AS REGARDS ADVANCED THERAPY MEDICINAL PRODUCTS

## OUTCOME OF THE PUBLIC CONSULTATION

This document summarises the contributions made by stakeholders to DG Enterprise and Industry's public consultation on proposals to amend Annex I to Directive 2001/83/EC as regards advanced therapy medicinal products conducted from 8 April to 10 June 2008. Stakeholders were invited to express their position on the basis of a public consultation paper[1].

### *Contributors*

The Commission received **44 contributions**. Some of them, in particular the ones from the industry, are the results of wider consultation. The participants can be classified into 6 categories: patients' organisations, academia and public organisations, industry (association and individual companies, including SMEs), regulatory authorities (EU, national and international), individuals, and other stakeholders. A list detailing all contributors is provided in the Annex to this document.

All contributions received provided valuable information and comments for the Commission's further action in this field.

### *Summary of contributions*

Overall, the proposal was supported in principle by all contributors. A number of detailed scientific comments were made on various aspects of the proposal. These technical contributions are not summarised in this document. However, several important non-technical comments also emerged:

[1] http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/advanced_keydoc.htm

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Flexibility vs. regulatory predictability:

A majority of stakeholders considered important that the Annex I to Directive 2001/83/EC only lays down high-level technical requirements, but does not go into the details of these requirements. The Annex I should then be supplemented by guidelines (from the European Medicines Agency or the European Commission). This approach was favoured to avoid setting up too strict legally-binding rules which might impair the development of products. A flexible approach also appeared necessary to accommodate new technologies.

On the other hand, a minority of stakeholders emphasised that the Annex I should provide a high level of regulatory predictability. Operators should know the requirements they are expected to meet in order to get a marketing authorisation for advanced therapy medicinal products.

Risk-based approach vs. prescriptive approach:

Industry stakeholders, in particular, welcomed the Commission risk-based approach as outlined in the public consultation paper, to determine the extent of characterisation in terms of quality, non-clinical and clinical data to be included in the marketing authorisation application. The fact that this risk analysis may cover the entire development, and that relevant available clinical data or experience with other, related advanced therapy medicinal products may also be considered, was also welcomed.

Definition of gene therapy medicinal products:

A large number of contributors commented on the proposed definition of gene therapy medicinal products (GTMPs). One contribution suggested to widen the definition in order to cover virtually anything that can tamper in a directed or targeted fashion with the human genome.

On the other hand, a large number of contributors voiced their concern about the proposed definition and requested to make it narrower. In particular, they suggested to exclude from the GTMP definition antisense products, siRNA, microRNA, double stranded DNA oligomers, ribozymes, aptamers, synthetic oligomers and other similar products. Various arguments were raised:

– In contrast to GTMPs, it was argued that such products are highly specific drugs whose mechanisms of action are not based on integration of novel genetic material into the patient's genome and expression of that material. Instead, they function by reducing or antagonizing specific RNAs, the products of gene transcription, a mechanism distinct from the mechanism of gene therapy.

– Such products behave like drugs insofar as their effects are transient and the reversibility of their effects is dependent on patients' metabolism.

– The current framework on gene therapy might be disadvantageous and could lead to a significant increase in production costs.

Several contributors also requested that prophylactic vaccines (*e.g.* cancer vaccines) involving the manipulation of genes or nucleic acid sequences, are excluded from the GTMP definition since they are already covered appropriately within the existing framework.

Borderline between somatic cell therapy and tissue engineering:

Several contributors highlighted that the borderline between somatic cell therapy and tissue engineering may not be fully clear, since the technical requirements suggested in the public consultation paper are relatively similar. A rule of demarcation was felt necessary. However, other stakeholders recalled that such a rule is already laid down in Regulation (EC) No 1394/2007 on advanced therapy medicinal products.

Other non-technical comments:

One contributor requested that the opportunity of the revision of Annex I to Directive 2001/83/EC is taken to introduce the concept of master file for excipients of biological nature.

Finally, one contributor requested that the legal text explicitly prohibits approval of any medicinal products that were studied or tested using embryos or embryonic tissue.

## Annex: list of contributors to the public consultation

**<u>Total:</u> 44 contributions**

**Patients' organisations (2 contributions)**

– Action Duchenne

– United Parent Projects Muscular Dystrophy

**Academia and public organisations (6 contributions)**

– European Network for the Advancement of Clinical Gene Transfer & Therapy: (CliniGene) jointly with the Regulatory Affairs and Ethics Committee of the European Society for Gene and Cell Therapy (ESGCT)

– Etablissement Français du sang

– IPFA (International Plasma Fractionation Association)

– Koch Institute for Integrative Cancer Research (formerly the Center for Cancer Research) at the Massachusetts Institute of Technology

– Leids Universitair Medisch Centrum

– North-East England Stem Cell Institute (NESCI)

**Industry (25 contributions)**

– Alnylam

– Archemix

– Avontec

– BIA (BioIndustry Association)

– BioSpring

– BPI (Bundesverband der Pharmazeutischen Industrie e. V.)

– Cellerix

– EBE-EFPIA (European Biopharmaceutical Enterprises)

– ERYtech Pharma

– Eucomed (European Medical Device Association)

– EuropaBio (European Association for Bioindustries)

– Giuliani Spa

– Isis Pharmaceuticals

– LFB Biotechnologies

– MedImmune

– Merck Sharp & Dohme (Europe) Inc.

– Merck Serono

– Novozymes

– Noxxon Pharma

– Pfizer

– RXi Pharmaceuticals

– Schering Plough

– Sylentis SAU

– TiGenix NV

– Topigen

**Regulatory authorities (7 contributions)**

– CS (State Institute for Drug Control)

– DE (Paul Ehrlich Institut)

– EMEA (European Medicines Agency)

– Non-EEA Regulatory Agency

– FR (Ministère de la Santé)

– NL (The National Institute for Public Health and the Environment (RIVM) and the Medicines Evaluation Board (MEB)

– UK (MHRA)

**Individuals (2 contributions)**

– Bill Marshall

– Claude Vella

**Others (2 contributions)**

– RNA Therapeutics Stakeholder Group

– Joint contribution of the University of Southampton, Bristol Institute for Transfusion Science and University of Bristol, Institut Curie, Inovio AS, Genvax