Merck Sharp & Dohme (Europe) Inc.
Clos du Lynx 5 Lynx Binnenhof
Brussel 1200 Bruxelles
☎ 32 2 776 6211

Angelika Joos
Associate Director
Regulatory Policy Europe
☎ +32 2 776 6432
Fax +32 2 776 6369
e-mail : angelika_joos@merck.com

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European Commission
DG Enterprise & Industry, Unit F2 'Pharmaceuticals'
.45 Avenue d'Auderghem, Office 10/128.
B-1049 Brussels
Att. of Nicolas Rossignol
e-mail: nicolas.rossignol@ec.europa.eu

Brussels, June 3, 2008

MSD Comments on the Implementation of the Advanced Therapies Regulation: public consultation on the revision of Annex I to Directive 2001/83/EC (Regulation (EC) No 1394/2007)

Dear Sir,

Enclosed are comments on the Implementation of the Advanced Therapies Regulation, which I am providing you on behalf of Merck Sharp & Dohme (Europe) Inc.
MSD (Europe) Inc. is an affiliate of Merck Research Laboratories (MRL) and Merck Manufacturing Division (MMD) in the US; MSD, MRL and MMD are all divisions of Merck & Co., Inc. (US).

Merck & Co., Inc. is a leading worldwide, human health products company with one of the leading biomedical research organizations. Our research division tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs and Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

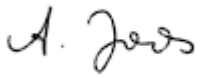
This concept paper has been reviewed in consultation with experts from our Safety Assessment, Bioprocess & Bioanalytical Research, Basic Research and Worldwide Regulatory Affairs departments.

Merck welcomes the initiatives to develop an effective, consistent, and efficient process for the evaluation of Advanced Therapies and supports a revision of the Annex I in order to adapt it to the specificities of advanced therapy medicinal products.
We propose to maintain the existing definition of gene therapy as currently specified in Directive 2003/63/EC (Annex to Directive 2001/83/EC) Part IV because the new

definition proposed for gene therapy medicinal products would cover not only the traditional gene therapy medicinal products as defined in Directive 2003/63/EC (Annex to Directive 2001/83/EC) Part IV, but also most oligonucleotide therapeutics (including siRNA, miRNA, and anti-sense oligonucleotide therapeutics). We believe, however, that these oligonucleotide therapeutics should not be regulated as gene therapy medicinal products. Our scientific justification for this position is presented in the attachment.

We appreciate the opportunity to comment on this document. Please do not hesitate to contact me, should you have any questions or wish to hold further discussions with our company experts.

Yours sincerely,



Angelika Joos

SUBMISSION OF COMMENTS ON PUBLIC CONSULTATION PAPER ON PROPOSALS TO AMEND ANNEX I TO DIRECTIVE 2001/83/EC AS REGARDS ADVANCED THERAPY MEDICINAL PRODUCTS

COMMENTS FROM Merck Sharp & Dohme (Europe) Inc.
GENERAL COMMENTS
None

SPECIFIC COMMENTS ON TEXT

SECTION

Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Section 2.2.1	Section 2.2.1 defines gene therapy medicinal product as "a medicinal product: - that contains or consists of a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and - whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence." This new definition would cover not only the traditional gene therapy medicinal products as defined in Directive 2003/63/EC (Annex to	We propose to maintain the existing definition of gene therapy as specified in Directive 2003/63/EC (Annex to Directive 2001/83/EC) Part IV: "For the purposes of this Annex, gene therapy medicinal product shall mean a product obtained through 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

[1] Where available

	Directive 2001/83/EC) Part IV, but also most oligonucleotide therapeutics (including siRNA, miRNA, and anti-sense oligonucleotide therapeutics). We believe, however, that these oligonucleotide therapeutics should not be regulated as gene therapy medicinal products. Our scientific justification for this position is presented below: 1) The effects of oligonucleotide therapeutics are short term and reversible (persists for hours to weeks), following which they are metabolized and cleared, whereas as the intended application of traditional gene therapy is for long term to permanent (persists for years to life) effects. 2) Concerns that have been raised with gene therapy medicinal products—e.g., replication, shedding, recombination, integration into somatic cells, integration into germ lines—are not applicable to the oligonucleotide therapeutics mentioned above. Non-clinical safety paradigms in support of clinical development therefore would differ considerably for traditional gene therapy compared to oligonucleotide therapy. For example, currently, integration and germline transmission studies are required for many vectors for traditional gene therapy products. These studies would not be applicable to oligonucleotide therapeutics. In addition, development of traditional gene therapy products do not require genotoxicity and safety pharmacology studies. In contrast, the current non-clinical safety testing for synthetic oligonucleotides generally includes genetoxcity testing of oligonucleotide therapeutics for a new type of oligonucleotide chemistry (though not required for new sequences), and safety pharmacology assessments are generally required to be performed within the toxicity studies.	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."

	3) The manufacture of oligonucleotides involves chemical synthesis, which is comparable to the process of manufacturing small molecule therapeutics. In contrast, traditional gene therapy products require biological manufacturing processes which involve cell culture and recombinant techniques. 4) Like small molecules, these compounds have better-defined chemical structures, better enabling characterization testing. 5) In addition, siRNAs typically contain modified bases, and are not native RNA molecules, further substantiating their similarity to small molecules.	