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to Nicolas Rossignol
European Commission,
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Unit F2 'Pharmaceuticals'
45 Avenue d'Auderghem, Office 10/128
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Belgium

our reference
your reference
date June 4, 2008
subject Proposal to Amend Annex I to Directive 2001/83/EC as Regards to Advanced Medicinal Products

Dear Mr. Rossignol,

This letter is in response to the Proposal to Amend Annex I to Directive 2001/83/EC as Regards to Advanced Medicinal Products.

The efforts to devise new standards for rapidly developing therapies are important, because maintaining the highest scientific standards for drug registration for these rapidly evolving technologies is critical and these therapeutics are an increasing part of our therapeutic armamentarium. Regrettably, the Proposed definition of genetic therapy, disregards well accepted definitions. The proposed definition of gene therapy includes any nucleic acid sequence "whose therapeutic effect is related to the sequence it contains". As a result, this definition of gene therapy now encompasses therapeutic nucleic acid sequences like antisense oligonucleotides whose activities are completely distinct from gene therapy. The proposed definition of gene therapy is based on the chemistry of the therapeutic rather than the mechanism of action.

The Commission's current definition of gene therapy is clear in defining a gene therapy medicinal product as one that "...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 current definition rightly acknowledges that in order for a nucleic acid sequence to be gene therapy it must be driven by an expression vector or promoter. On the basis of the current definition antisense therapeutics that lack promoters would be appropriately excluded from the definition of gene therapy. In contrast, under the proposed definition they would be labeled as gene therapy despite the fact that their mechanism of action is directed toward RNA not genomic DNA, and despite the fact that there is no mechanism for them to be incorporated into DNA or produce heritable effects as a result of integration with the genome.

Although antisense therapeutics are nucleic acid-based, their activities and pharmacology are typical of tradition pharmaceuticals. Their activity is completely dependent on their temporal presence in cells and their activity wanes as the nucleic acid-based drugs are metabolized by nucleases and cleared from the body. This is in contrast to true gene therapy medicinal products that can become integrated into the genome and produce permanent changes to the genome or be shed or self-

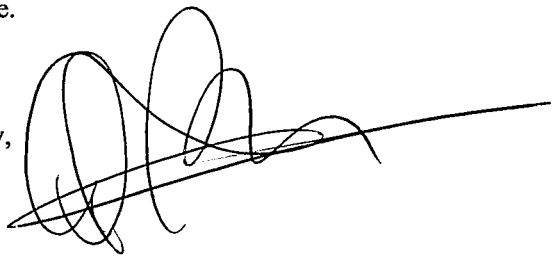
replicate. As molecular biologists and pharmacologists, we see antisense therapeutics are strikingly different from gene therapy and believe that misusing the label of gene therapy on these types of therapeutics will get in the way of important new therapeutic agents for patients.

As an example, our research into Duchenne's muscular dystrophy has led to a novel approach that uses antisense oligonucleotides to treat this fatal disease. This approach is quite distinct from vector-mediated gene therapy, in that no attempt is being made to insert new genetic material. In fact, the antisense approach successfully inhibits the portions of miscoded RNAs to achieve the synthesis of a functional protein (New England Journal of Medicine (2007) 357:2719). Calling this 'gene therapy' would needlessly complicate the already complicated registration process for drugs, without adding anything relevant to the safety monitoring of patients. More importantly it would be imposing regulations that are not based on scientific rationale.

The public policy implications for adopting regulations based on faulty science are enormous. Not only would the regulatory aspects ad more complexity and thus delay for promising biotech solutions. But also the often are the difference between success and failure due to stringent financing windows. Finally, ill-founded regulation would generate major outcry amongst the patient communities which stand to benefit from antisense therapeutics. This notably applies to a great variety of rare diseases, where the small patient numbers require multi-centric and multinational trials. Especially these would be disproportionally hindered by scientifically incorrect definitions as they will be translated differently into laws by different member states.

In conclusion, we respectfully request that the Proposed definition be amended reflect the best possible science.

Yours sincerely,



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