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Mr. Nicolas Rossignol
European Commission
DG Enterprise & Industry, Unit F2 'Pharmaceuticals'
45 Avenue d'Auderghem, Office 10/128
B-1049 Brussels, Belgium

Dear Mr. Rossignol,

Recent advances in molecular biology are the basis for novel and promising therapeutic agents. These advanced therapeutics should be regulated with equally advanced understanding by the authorities that are responsible for assuring the safety of new medicines. Anything less may deprive patients of benefits that science can now offer.

This letter serves as a comment to the "Proposals to amend Annex I to Directive 2001/83/EC as regards to the Advanced Therapy Medicinal Products" (issued by the European Commission, Enterprise and Industry Directorate-General, for Implementation of the 'Advanced Therapies' Regulation [*(EC) no 1394/2007]*).

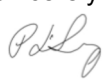
In particular, we are concerned about the proposed definition of a gene therapy medicinal product (Section 2.2.2), which is stated as "a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and as any therapeutic whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains…" This definition is over-inclusive and will inappropriately categorize all oligonucleotide-based therapeutics (short interfering RNAs [siRNAs], antisense, and microRNA targeting oligonucleotides) as gene therapies.

Gene therapy should be a term reserved for therapeutic modalities that affect change by adding genetic material that is expressed by cellular machinery to supplement or replace a gene product. In contrast, oligonucleotide-based therapeutics 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; this is a mechanism clearly distinct from the mechanism of gene therapy. Under the proposed definition, these oligonucleotide-based therapeutics would be labeled and regulated as gene therapy agents because their mechanism of action is sequence-dependent. However, since they are not embedded in expression vectors, the oligonucleotides are not functional genetic material that can insert, replicate, be transcribed, or otherwise effect change in the genome, and would not by any other definition be considered genetic therapy. Oligonucleotide therapeutics have been widely shown to have transient drug-like pharmacologic effects that reverse when the agent is cleared.

To label all oligonucleotide therapeutics as gene therapy is potentially misleading, and will propagate misunderstanding, thus diminishing the scientific rigor of the regulatory process. Ultimately, this mislabeling will impede the development of new therapeutics using these important technologies and may even create inappropriate alarm and misgivings in patients who could benefit the most from these kinds of novel therapies.

We are moved to comment on this issue because the proposed changes to the definition of gene therapies are coming at a time when knowledge stemming from the discoveries surrounding siRNA and microRNAs promise to change the way we understand disease processes, and how we treat diseases. We believe that the inappropriate classification of all oligonucleotide therapeutics as gene therapy threatens to hamper the application of our newly acquired knowledge. It serves neither patient safety nor public health and wellbeing.

Sincerely yours,



Phillip A. Sharp and the signatories as shown in the attached pages