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To the kind att. of
Dr. Nicholas Rossignol
European Commission
DG Enterprise and Industry,
Unit F2, "Pharmaceuticals"
Office 10/128
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Belgium

Milan, May 29th 2008

Re: **Implementation of the "Advanced Therapies" Regulation**
Regulation (EC) No. 1394/2007

We are pleased to have the opportunity to provide comments on the proposed implementation of the "Advance Therapies" Regulation (EC) No. 1394/2007.

In Section 2.2.1, the definition of "Gene Therapy Medicinal Product" is described 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", which appears to include synthetic oligonucleotides.

We believe that antisense oligonucleotide drugs, which are short nucleic acid sequences manufactured by chemical synthesis, should be specifically excluded from the proposed definition of Gene Therapy Medicinal Product.

Antisense oligonucleotides are chemically synthesized using commercially available automated DNA synthesizers. The manufacturing process is similar to that of synthetic peptides, comprising of solid phase oligonucleotide synthesis, cleavage of the crude protected oligonucleotide from the solid support, deprotection, preparative chromatographic purification and lyophilization to yield the drug substance. As such, this class of synthetic drugs is qualitatively different from gene therapy medicinal products, and we believe that it is inappropriate to regard these as belonging to the same category of products.

In fact, there is historic precedence for the regulation of oligonucleotides as chemical entities in Europe with the approval of Vitravene™, an antisense oligonucleotide for treatment of cytoMegalovirus retinitis (CMV), and Macugen™, a pegylated aptamer approved for treatment of age-related maculardegeneration (AMD).

Pharmacologically, antisense oligonucleotides are designed to hybridize to their messenger RNA complement and thereby down-regulate production of the relevant protein. They are typically short sequences of DNA or RNA, typically less than 30 nucleotides in length. Hence, they are far too short to code for any functional peptide products, and they do not contain proper flanking regions to support translation into amino acid sequences. In addition, after hybridization of an

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antisense oligonucleotide to its target mRNA sequence, the double-stranded structure is recognized as abnormal and is cleaved by cellular enzymes (such as RNAse H), thereby achieving the destruction of the mRNA, as intended, via this antisense mechanism. By contrast, gene therapy products contain sequences of vastly greater length that code for entire known proteins, with flanking regions and promoters, as well as various types of vectors, to facilitate the intended transcription and translation into the desired protein.

Although questions have been raised over the years about the potential for the short DNA segments of antisense oligonucleotides to be somehow incorporated into the genome by insertion or exchange events (perhaps during cell division), to our knowledge, there have never been any actual reports of this occurring in biological systems. Along these same lines, the possibility that monomeric nucleotides derived from oligonucleotides might be metabolically incorporated into DNA and cause transcription mutations is also extremely implausible and not consistent with known biochemistry (e.g., it is incompatible with the known substrate specificity of DNA polymerase enzymes). As a testimonial to the absence of any mutation-inducing property of oligonucleotides, this class of molecules has been shown to be consistently negative in short-term tests for genotoxicity, to an extent that led to the proposal from the EMEA that oligonucleotides should be considered for exemption from genetic toxicity testing.* Furthermore, it is well known that oligonucleotides are degraded by the variety of cellular nucleases present within cells, and they do not persist for an extended period of time. Thus, the biological disposition and behavior of oligonucleotides within cells is distinctly different from gene therapy products, and the only common element is simply the nucleotide units that constitute these molecular entities. To categorize them in the manner in terms regulatory policy would be akin to treating short synthetic peptide receptor antagonists and human protein growth factors in the same manner because they both consist of amino acids.

Clearly, there is a vast difference between antisense oligonucleotides and gene therapy products with regard to their method of manufacture, their size, their intended action and basic biological properties, and their regulatory history. In light of these differences, we believe that the proposal for regulation of oligonucleotides in the same manner as gene therapy products is unsound.

If you have any questions regarding our comments, please contact me.

Sincerely yours,

Dr. Mario Germano Giuliani
President
Giuliani S.p.A.

* CHMP SWP Reflection Paper on the Assessment of the Genotoxic Potential of Antisense Oligodeoxynucleotides, European Medicines Agency Pre-authorization Evaluation of Medicines for Human Use, London, 20 January 2005 (Doc. Ref.EMEA/CHMP/SWP/199726/2004)