ISIS
PHARMACEUTICALS

1896 Rutherford Road Carlsbad, CA 92008
p 760.931.9200 f 760.603.4650 www.isispharm.com info@isisph.com

June 8, 2008

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

RE: Comments on the Proposed Change in Gene Therapy Definition in the Advanced Therapeutics Amendment

Dear Sir or Madam:

Isis Pharmaceuticals, Inc. is a leading innovator in the discovery and development of novel synthetic antisense oligonucleotides. Since 1989, Isis has focused on the characterization, manufacture and clinical development of this therapeutic class of drug product. For these reasons, Isis is well-qualified to comment on the Public Consultation Paper entitled *Proposals To Amend ANNEX I To Directive 2001/83/EC as Regards Advanced Therapy Medicinal Products* dated April 8, 2008. Comments are being provided here to the European Commission Enterprise and Industry Directorate-General on the proposed revisions in the definition for *Gene therapy medicinal product* described in Section 2.2.1 of the proposed amendment.

Executive Summary

We believe the proposed revision to the definition of gene therapy inappropriately classifies antisense oligonucleotides, including siRNA, as well as olignucleotide aptamers as gene therapy, when mechanistically they are very different. The current definition of gene therapy medicinal product [1] is accurate and appropriate, reflective of the underlying mechanism of action and mode of manufacture of this class of products. This definition was the consensus position that resulted from significant discussions between scientific and policy experts and regulatory agencies in 2002/2003. The current definition is actionable and it has served the public interest in distinguishing between products based upon gene transfer technology and conventional pharmaceutical products in order to justify gene therapy medicinal products being regulated under a special regulatory regime under the head of "Advanced Therapy Medicinal Products".

[1] As defined in Annex I of Directive 2001/83/EC, as amended, a 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 proposed revision to the definition of gene therapy is inappropriate and lacks precision. The language as drafted is too broad, inaccurate and confuses drugs that are designed to interact pharmacologically with RNA, with genes designed to be introduced into cells to alter permanently or semi-permanently the genotype of the cell. Moreover, it is incompatible with the World Health Organization's position that antisense oligonucleotides are not members of the gene therapy product class.

Antisense oligonucleotides, including siRNA molecules, are dramatically different from genes for the following scientific reasons. Antisense oligonucleotides, at 7,000 Daltons are relatively small molecules compared to genes which are typically a million Daltons or more, and are embedded in plasmids that are much larger. Genes are synthesized biologically and are properly considered biological agents. Antisense drugs are chemically synthesized, chemically modified and chemically analyzed. Genes are designed to be integrated into genomes and be transcribed into RNA to result in a protein. Thus, they must have all the elements necessary to assure proper genomic insertion and performance. Antisense drugs are designed to interact with RNA, are not integrated into the genome, and lack the elements necessary to make them functioning genes. Genes must be delivered in vectors, such as viruses or in cationic liposomes. Antisense drugs are typically delivered in saline. Genes are designed to result in prolonged effects. Antisense drugs are cleared by metabolism and the duration of their effects correlate with their pharmacokinetics.

Perhaps most importantly, in studies in many thousands of patients extending for several years of treatment, antisense drugs have proven to be reasonably well tolerated and to display dose dependent efficacy and safety. Gene therapy has had a very different clinical experience.

In conclusion, we believe the current definition of gene therapy is accurate and serves the public interest. The proposed definition is inaccurate, would dilute the appropriate focus on gene therapy and is to contrary to public interest.

Gene Therapy Practice and Current Definition

Gene therapy is principally the practice of inserting a large piece of double-stranded DNA directly into cells for the purpose of correcting, replacing or supplementing a gene that is involved in a disease process. As such, gene therapy can be considered as a 'gain of function' manipulation of the genome. Whether insertion of gene is somatic or germ-line transmission, there are a number of technical aspects that are unique to gene therapy and not relevant to other types of oligonucleotide-based therapies (see Table 1). The use of a vector system, such as a virus, to incorporate a large piece of DNA into the genome is the most salient feature that distinguishes gene therapy from other oligonucleotide based therapies. A gene therapy agent typically contains all of the elements necessary to be transcribed, and stably express the therapeutic gene product in patients. This is not the case for antisense or siRNA therapeutics and the current definition properly recognizes that distinction. We respectfully submit that the current definition remains scientifically

justified and appropriately serves as the basis for regulations and approvals. Adopting a definition of gene therapy that is simply based nucleic acid sequence-dependent activity would require inappropriate hurdles for the initiation of clinical trials and specialized follow-up procedures that differentiate the non-clinical and clinical monitoring of gene therapy products from other drugs. We believe that the definition ought to be reflective of the differentiated characteristics associated with the incorporation of a functional genetic unit driven by a promoter or expression system.

Table 1. Notable Differences Between Antisense oligonucleotides* and Gene Therapy

Parameter	Antisense Oligonucleotide	Gene Therapy
Size	18 to 22 nucleotides (~7,000 dalton)	1,000 to 10,000's base pairs (≥1,000,000 dalton)
Manufacture	Chemically synthesized and purified	Expressed using recombinant DNA technology
Chemistry	Single strand composed of native DNA and/or chemically modified RNA with phosphorothioate linkages	Native double stranded DNA
Receptor	mRNA	Genomic DNA
Regulation	No regulatory elements	Contains regulatory elements
Consequence	Decreased expression of target protein	Increased expression of protein
Delivery	Saline solution	Requires viral vector or liposome
Duration of Action	Transient	Stable incorporation and expression
Clearance	Metabolic degradation	Prolonged effect

*Properties tabulated are specific to single stranded antisense inhibitors. The basic properties are essentially the same for siRNA except that they are double stranded RNA (approx. 14,000 Da) and some times employ liposomes to enhance delivery.

The only cases in which a small oligonucleotide therapeutic should be considered a gene therapy medicinal product are those instances in which the antisense or shRNA are administered within a plasmid capable of expression and sustained transcription. These applications are differentiated from other antisense or siRNA applications because of the presence of the expression system. Under both the present definition, these expressed antisense or shRNA agents fit the definition of gene therapy and should be regulated as such.

Antisense Oligonucleotides are Distinct from Gene Therapy Products

A detailed set of arguments to exclude synthetic oligonucleotide drugs, including antisense inhibitors, from the gene therapy definition is set forth below. An exclusion of

antisense oligonucleotides from the definition outlined in Section 2.2.1 of the Proposal is justified on the basis that antisense inhibitors do not involve any recombinant DNA technology (such as plasmids or regulatory elements to control their expression), and they do not use viral vectors either in their delivery or in their mechanism of action. Like small molecules they are synthetic drugs in every sense and are not functional genetic units. Chemically synthesized oligonucleotides are typically 20 nucleotides long or less (approximately 7,000 daltons), and do not possess the regulatory elements necessary for genomic incorporation or amplification. Thus, a short sequence of 20 oligonucleotides does not provide sufficient genetic information to constitute a gene.

The pharmacokinetic, metabolic, and pharmacologic properties of antisense oligonucleotides also make them distinct from Gene Therapy. Antisense oligonucleotides are akin to traditional synthetically-manufactured drugs except that they happen to share some of the chemistry of nucleic acids. Much like small molecules, antisense oligonucleotides bind to a receptor, mRNA, and like drugs, the interaction is transient. The pharmacologic consequence of antisense binding to its target is reduction in translation to protein. Oligonucleotide drugs are metabolized and cleared from the body, and thus, like small molecules, their pharmacology is transient and repeated administration is required.

The chemical composition of antisense oligonucleotides is distinct from genes in that they are small, single stranded DNA or RNA containing modified sugars and modified internucleotide linkages that are not found in nature, and thus, are not incorporated into the genome. In fact, the regulatory requirements for Chemistry, Manufacturing and Controls (CMC) for these drug products are distinct from those for Gene Therapy Products, and like those for short synthetic oligopeptides, closely follow those applied to traditional small molecule drugs. Moreover, the requirement for development genetics, which is central to the design and characterization of gene therapy medicinal products, is neither relevant nor applicable to antisense oligonucleotides. Manufacture of gene therapy products is based upon the principles of establishing a common source material generally known as cell bank or seed lot to ensure product consistency, e.g. viral vector for gene transfer or bacteria to produce plasmid DNA. This requirement for establishing a cell bank or common seed lot is not applicable or relevant to chemically synthesized antisense products.

We believe the current regulatory position regarding these requirements is an appropriate one, as it reflects accurately the wholly synthetic nature of oligonucleotide manufacturing, the well-defined nature of the product and the analytical control strategies employed. The proposed revision to the current definition of gene therapy would seem to presage an inappropriate drift in regulatory thinking toward applying CMC requirements for biologics to synthetic oligonucleotides. In contrast to short synthetic oligonucleotides, biologics are not manufactured synthetically and are generally not well characterized.

Guidelines for Safety Monitoring of Gene Therapy are Not Appropriate for Antisense Oligonucleotides

The guidelines for special consideration in monitoring of nonclinical and clinical studies for Gene Therapy Products focus on the genomic incorporation of active expression of the gene, germ-line transmission, shedding of gene or vector, and long-term persistence or follow-up. However, none of these properties is relevant to antisense inhibitors. Below, the known properties of antisense oligonucleotides, including siRNA, are used to illustrate that the guidelines for monitoring gene therapy products have no relevance to the short synthetic and chemically-modified oligonucleotide sequences that have been employed for the past 15 years as antisense drugs.

No germ-line transmission:

- Oligonucleotides like antisense drugs are not integrated into the genome. Their effects diminish as they are cleared through metabolism. This degradation of the antisense agents over time makes it impossible to have germ-line transmission. Because of absence of an expression system and because of the known metabolic clearance, antisense agents do not have the potential to be heritable, and thus germ-line transmission is not a risk.
- Germ-line transmission is also restricted because there is little to no distribution to germ-line cells. What oligonucleotide is measurable in testes has been shown by immunohistochemical technique to reside in the stromal tissue and resident macrophages, but does not cross the blood-testes barrier.

No incorporation of short oligonucleotides:

- Antisense inhibitors are single stranded DNA and do not employ viral vectors to facilitate incorporation or to induce amplification of the antisense sequence. Antisense oligonucleotides will not replicate nor can they be replicated by the cellular machinery because they lack sequence elements, such as promoters or enhancers, required for replication.
- Single stranded DNA oligonucleotides can not be directly incorporated and double stranded RNA oligonucleotides of 18 to 20-residues are too small to be incorporated into the genome through homologous recombination (Coffin, 1990). The minimum size of a DNA for homologous recombination is 400 to 500 residues (Bollag et al., 1989; Lai and Lien, 1999)

No expression of antisense oligonucleotides:

- Since oligonucleotides can not be incorporated into the genome, they are not transcribed by the normal cellular process as they are not double stranded and are too short to bind to the RNA polymerase complex.
- Short oligonucleotide sequences also are too short to possess the regulator sequence elements necessary for replication or expression.

No shedding of antisense oligonucleotides:

- Antisense oligonucleotides, including siRNA are metabolized by exonucleases and endonucleases that are present in plasma and all cells. Mass balance pharmacokinetic studies can account for 80 to 90% of the administered dose and metabolites are detected in urine (Geary et al., 2001). Other evidence of catabolism is also observed. Furthermore, since viral vectors are not used in the delivery of antisense oligonucleotides, there is no shedding of vector or expressed gene.

No long-term persistence in cell or tissue:

- It is a well established property of antisense oligonucleotides that they are metabolized and cleared much like traditional small molecules (Geary et al., 1997; Geary et al., 2001; Phillips et al., 1997). They are degraded and eliminated by endonuclease/exonuclease-mediated metabolism (Geary et al., 2007). The half-life of modified phosphorothioate oligonucleotides may be as long as several weeks, but still there is finite residence time after which the pharmacologic effects are reversed (Geary, 2002). Both non-clinical and clinical studies are designed to thoroughly characterize the clearance, elimination, and reversibility of oligonucleotide exposure and effect.
- For antisense oligonucleotides, pharmacologic activity is dependent on intact oligonucleotide concentration in tissues, and the duration of action parallels the clearance of oligonucleotide from tissue (Kastelein et al., 2006; Yu et al., 2002; Yu et al., 2006; Yu et al., 2007). The pharmacodynamic relationship has been documented for a number of antisense oligonucleotides in both animals and humans. Clinical trials are currently designed to monitor patients for an appropriate amount of time based on the half-life properties. Typically the follow-up period is 3 to 5 half-lives. Because of this finite residence time in patients, there is no need for extended long-term follow-up past the point of clearance.

Proposed Definition is Inconsistent with Established WHO Policy on Medicinal Product Nomenclature and Broader Community Policies

The WHO Nomenclature Committee has recently completed and adopted its scientific review on international nonproprietary names (INNs) for biological and biotechnological substances. To facilitate consistent and predictive use of medicinal products based on non-proprietary names, the WHO indicates that the existence of a consistent INN system is important for clear product identification; safe prescription and dispensing of medicines to patients and communication and exchange of information among health professional and scientists worldwide. The WHO also makes clear in various policy documents that antisense oligonucleotides are pharmacologically and structurally distinguishable from gene therapy products and as such they are described by a different naming system. According to the INN Working Document 05.179 (8 November 2007), antisense oligonucleotides are described by using the common stem "-rsen", e.g.

ofovirsen, cenersen. Distinguishable from the naming system for antisense oligonucleotides, INNs for all gene therapy products are described using the so-called "Two-Word Scheme". Word 1 describes the gene component. e.g. -ermin for growth factor, -tusu- for tumor suppression. Word 2 describes the vector component. e.g. -adeno- for adenovirus, -herpa- for herpes virus whereas the suffix refers to whether the vector is replicating competent, e.g. -vec for non-replicating viral vector, -repvec for replicating viral vector, -plasmid for plasmid vector. If Annex I were to be amended to re-classify anti-sense oligonucleotides as gene therapy medicinal products, it would inevitably cause unnecessary confusion. It is the legal obligation for the Commission to ensure that amendment to Annex I is consistent with the requirements set out in Directive 2001/83/EC. In this case, Community law requires the Commission to have regard to the WHO INN policy in preparing the proposed legislative instrument.

One of the key commitments made by the Commission, as set out in its publication "Life Sciences and Biotechnology - A Strategy for Europe", is to respond to global challenges by developing the EU domestic policies with a clear international perspective. We respectfully submit that the proposed definition for gene therapy medicinal product has failed to meet this Community commitment as it ignores the position agreed internationally by the WHO as regards the differentiation between anti-sense oligonucleotides and gene therapy products.

Most critically, consistent with the broader Lisbon Agenda and the adopted policy for better Community Governance, the proposed legislation should be firmly based upon sound scientific principles in order to ensure delivery of effective, credible and responsible regulatory policies which instill confidence and support of the general public and the key stakeholders from the scientific community and the commercial sector. For the reasons given above, we respectfully submit that there is no proper scientific basis to justify a change to the current definition for Gene Therapy Medicinal Product.

Conclusions and Recommendations

Based on the points raised in this document we believe the definition of Gene Therapy should distinguish between gene therapy and antisense oligonucleotides, including siRNA. Regulations that do not make this distinction would not serve the public interest and would hamper innovation because the monitoring and pharmcovigilance required for gene therapy products are very different than those recommended for other drugs. Antisense and RNA-targeting drugs are clearly distinct from gene therapy and should not be regulated the same as gene therapy medicinal products. Antisense can fairly be characterized as Advanced Medicines, but should have an independent set of guidelines that reflect their specific properties. .

It is our recommendation that the current definition of gene therapy medicinal products should be retained, or that the new definition be modified to clearly require the use of a delivery vector or plasmid system with the purpose of insertion and stable expression of a specific gene as the key essential elements of the definition. Furthermore, we believe that

this legislative position is consistent with that already adopted by the WHO in its INN naming procedure for biological and biotechnological substances.

We welcome the opportunity to discuss the positions outlined above further. Please feel free to contact us at + 760 931-9200.

Sincerely,

Jeffrey M. Jonas
Executive Vice President, Development

Scott Henry
Vice President, Toxicology

Joseph F. Johnston
Executive Director, Regulatory Affairs

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