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Madrid, 6 June 2008

Comments on Public Consultation on Proposal to Amend Annex I to Directive 2001/83/EC as Regards advanced Therapy Medicinal Products

Dear Mr. Rossignol,

We sincerely thanks you for giving us the opportunity to comment about the Public Consultation Paper entitled "Proposal to amend Annex I to Directive 2001/83/EC as Regards Advanced Therapy Medicinal Products" *Regulation (EC) No 1394/2007*

Comment:

Oligonucleotides manufactured by chemical synthesis should be excluded from the definition of gene transfer medicinal product proposed to amend Directive 2001/83/EC:

Page 5. "Point 2.2. Definitions:

2.2.1. Gene therapy medicinal products:

Means 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 sequence it contains, or to the product of genetic expression of this sequence."

Rational:

1.- Protection of public and animal health:

- Advanced Therapy Medicinal Products, of gene therapy (GT) and somatic cell therapy (SCT) needs to comply with the necessary requirements of quality and safety in order to safeguard public health and to prevent the transmission of diseases and of infectious genetically modified organisms. These diseases are inherent to GT and SCT products: Biologics contain complex active substances manufactured in living systems. This risk does not exist in entities (active substances) obtained (synthesized, developed and manufactured) by Chemical Synthesis.

2.- Manufacturing process - Drug Substance

- We consider Oligonucleotides manufactured by chemical synthesis "mimics" the biological product -a nucleic acid sequence- but are obtained by chemical synthesis (not in living systems) so regulatory and technical requirements are in the way that New Chemical Entities, according the Directive 2001/83/EC, Directive 2001/20/EC (GCP) and Directive 2003/94/EC (GMP).
  The manufacturing process of this chemical entity is well-understood and controlled and provides sufficient physical - chemical characterization of the drug product.

3.- Mechanism of action

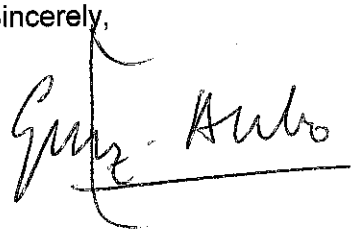
- Oligonucleotides interfere in the expression of specific genes, by inhibition of the mRNA. They do not penetrate into the nucleus of the cells, acting at the cytoplasm level, similar to most marketed products.

4.- Regulatory:

- One of the main tasks carried out by the EMEA together with other regulatory Agency (members of ICH) is to promote international harmonization of the requirements for registration of pharmaceuticals among the three regions EU, USA and Japan so that the drug products are developed and made available to promote public heath, preventing unnecessary duplication of clinical trials in humans, and minimizing the use of animal testing.
  Consequently It has no sense that the same compound follows different regulations in the different regions depending on different drug classification (as biological or chemical entity).
  This gene - therapy definition will therefore fall out of the proposed principle of harmonization.

Sylentis SAU appreciates the opportunity to comment on the consultation document.

Yours Sincerely,



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