MedImmune

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RE: Proposals to Amend Annex 1 to Directive 2001/83 as regards Advanced Therapy Medicinal Products, dated 8 April 2008

Dear Sir:

MedImmune appreciates the opportunity to submit comments regarding the public consultation paper "Proposals to amend Annex 1 to Directive 2001/83 as regards Advanced Therapy Medicinal Products, dated 8 April 2008". MedImmune is wholly owned by AstraZeneca plc and is the worldwide biologics business for the AstraZeneca Group. The company has approximately 3,000 employees worldwide and is headquartered in Gaithersburg, Maryland. Dedicated to advancing science and medicine to help people live better lives, the company is focused on therapeutic areas that include infection, oncology, respiratory disease and inflammation, cardiovascular/gastrointestinal disease and neuroscience.

MedImmune strongly feels that prophylactic attenuated viral vaccines are not Gene Therapy Medicinal Product and are appropriately regulated through the current processes already. Further discussion and commentary are provided below.

Background and Problem Statement: Vaccines are currently regulated in the European Union as medicinal products within the scope of Directive 2001/83/EC. Marketing authorisation of these products is subject to review and approval by European Union authorities and individual batches are also subject to Official Control Authority Batch Release (OCABR). Live viral vaccines that are the product of biotechnology may in addition be considered Genetically Modified Organisms (GMO's), which require separate national competent authority review according to Directive 2001/18/EC.

As of December 2008, Regulation 1394/2007 on advanced therapy medicinal products will come into force. This legislation is intended to improve regulation of complex products such as gene therapies and to ensure that certain products, previously not captured by the European regulatory framework, are now subject to appropriate controls. The possibility has been raised that some viral vaccines may be considered advanced therapy products and so subject to requirements of the new legislation.

Considerations relative to Gene Therapy Medicinal Products: The current definition of a Gene Therapy Medicinal Product is given in Annex I of Directive 2001/83/EC:

[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.

When considering the term 'prophylactic', this wording could be interpreted to capture an attenuated viral vaccine. This would include products such as FluMist (approved in the US) and also Zostavax and Rotarix. However, when this definition was first published, the preamble (point 10) to the amending directive (2003/63/EC) stated:

"In so far as they achieve their essential action through metabolic, physiological and immunological means to restore, correct or modify physiological functions in humans, these novel complex therapeutic products representing a new category of biological medicinal products."

A prophylactic vaccine with a conventional therapeutic indication performs no such physiological functions and fits poorly within this new category. The Annex I text makes no mention of vaccines in the context of advanced therapies. So while the current definition may inadvertently capture a viral vaccine manufactured using recombinant DNA methods, it is unlikely that this was the original intention of the legislation.

Following implementation of the advanced therapies Regulation 1394/2007, modification of this definition has been proposed (consultation paper of 8 April 2008):

Gene therapy medicinal Product ... 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 acid sequence it contains, or to the product of genetic expression of this sequence.*

A gene therapy should satisfy both criteria according to this proposal. Prophylactic vaccines with a conventional therapeutic indication, as a class, would not meet the first criterion and therefore would not be considered gene therapy products. In addition, Regulation 1394/2007 calls for guidance to ensure proportional application of the new requirements. In the absence of such guidance, it is considered that regulation of prophylactic attenuated vaccines as gene therapies would not be proportional to the associated risks. This situation would benefit from clarification.

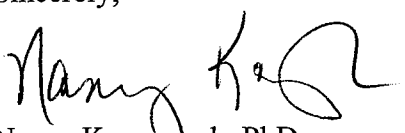
Prophylactic vaccines have been an important tool in protecting the public health throughout the world. For vaccines to have the greatest impact on health, they must have a reassuring safety profile to assure wide acceptance and use. This assurance is provided within the current legislation on vaccines under Directive 2001/83/EC and associated

EMEA guidance on vaccines. Further assurance of product quality and safety is provided within the OCABR and GMO deliberate release mechanisms (where relevant).

Conclusion: Prophylactic attenuated vaccines are currently regulated through an appropriate and proportional system. Further regulation as gene therapy products would not be consistent with the original intentions of the advanced therapies legislation. Regulation of both vaccines and gene therapies would be best served by clarification of this aspect in forthcoming amendments to Directive 2001/83/EC. In the absence of clarification, regulation of recombinant attenuated vaccines as gene therapies could adversely impact the benefit new vaccines could bring to the European population.

We greatly appreciate the opportunity to comment on "Proposals to amend Annex 1 to Directive 2001/83 as regards Advanced Therapy Medicinal Products, dated 8 April 2008" and would be willing to provide additional information if requested. We would also be grateful to be included in future discussions about development of the amendment.

Sincerely;



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