Mr Nicolas Rossignol
European Commission
Enterprise DG, Pharmaceuticals, Unit F2
EUROPEAN COMMISSION, AN88 1/06
B-1049 Bruxelles
Belgium

novozymes®
Rethink Tomorrow

15 May 2008

Dear Mr Rossignol,

Response to request for contributions on the European Commission's proposals to amend Annex I to Directive 2001/83/EC as regards Advanced Therapy Medicinal Products

On behalf of Novozymes Biopharma UK Ltd, I am writing in response to the European Commission's request for comments on their recent proposals for revision of Part IV of Annex I to Directive 2001/83/EC that were released for public comment last month. Novozymes Biopharma welcomes this opportunity to provide its input into this debate as a supplier of high quality, animal-free pharmaceutical components, such as the novel biotechnological excipient Recombumin® (yeast-derived recombinant human albumin), to medicinal product manufacturers.

You will recall from our preceding correspondence that Recombumin® is used as a replacement for plasma-derived human serum albumin in the formulation of protein-based pharmaceutical products and is aimed at enhancing patient safety. Novozymes Biopharma believes that the provision of such high purity, quality and consistent biological components for use as raw materials in the manufacture of Advanced Therapy Medicinal Products (ATMPs) is critical. However, as discussed in earlier communications, we have experienced logistical difficulties in providing information relating to Recombumin® to the EMEA as we are unable to use the master file system to protect our proprietary manufacturing know-how, as we have in other countries. The restrictive European legislation in this area has hampered our ability to undertake collaborative research and development of novel biological products in Europe. We understand that other small and medium sized enterprises (SMEs) have also experienced similar difficulties due to the limitations of the EU master file system.

Novozymes Biopharma believes that the current regulatory position on the European master file system (i.e. excluding its use for novel excipients and substances of biological and biotechnological origin) impedes SMEs' ability to undertake the development of innovative medicinal products in the EU. In our view, these constraints could have a direct negative impact on pharma manufacturers including those developing ATMPS.

We would like to take this opportunity to re-iterate some of the points that we have presented previously that we regard as crucial for the successful implementation of the ATMP regulation. We consider it critically important that the Commission addresses the inter-related issues as discussed below in the context of proposed revisions to Annex I to Directive 2001/83/EC.

Novozymes Biopharma believes that a workable and flexible master file system aimed at protecting commercially sensitive information is a fundamental part of creating a regulatory environment that both fosters innovation and that can also accommodate advanced therapy products. Many ATMPs are developed through collaborative efforts between companies, often SMEs, for whom protection of proprietary know-how is critically important. The lack of an EU master file system severely limits the intellectual property protection available to these SMEs for whom patent filing and enforcement may not be a viable option.

Telephone:
++44 115 9551245

E-mail:
kden@novozymes.com

Novozymes Biopharma UK Ltd
Castle Court
59 Castle Boulevard
Nottingham
NG7 1FD UK
VAT No. GB 660 6494 23
Registered No. 1142208 England

Novel excipients and biological/biotechnological substances play an integral part in the development of advanced therapies. They serve as raw and starting materials in the production processes for ATMPs or as formulation aids in the final presentation, with many of these components being manufactured by SMEs. Accordingly we believe that there is an urgent need to revise paragraph 3.2.2.4(d) Annex I to Directive 2001/83/EC as amended to expressly permit the use of the master file system for these substances. We feel that this would benefit a large proportion of the pharmaceutical industry, including ATMP manufacturers and especially SMEs, by reducing the barrier to innovation in this area and bringing Europe in line with other global markets.

In the Commission's consultation paper of May 2005 discussing their proposals for a community regulatory framework for ATMPs, the EC acknowledges the benefits of centralised assessment of both biotechnology-derived and advanced therapy products. Such an approach enables the pooling of scientific expertise from all member states to guarantee a high level of scientific evaluation across the EU. In our view, this can only work effectively if the novel/biological components that are involved in the production processes of ATMPs are also centrally assessed by allowing the manufacturers of these components to file master files directly with the EMEA. This system would enable direct dialogue between the manufacturers and the agency thus ensuring that reviewers have access to the most knowledgable experts and comprehensive information on the component's manufacturing process and product characteristics. We would suggest that such a strategy is likely to enhance the safety evaluation of the ATMPs in which they are used.

The Commission has indicated previously[1] to Novozymes Biopharma that it would consider our proposal to extend the master file concept to novel biological/biotechnological excipients for the next revision of Annex I to Directive 2001/83/EC as amended in line with the implementation of the ATMP Regulation (EC) No 1394/2007. Subsequently the Commission published its ATMP Regulation Implementation Plan in December 2007 and more recently its public consultation paper requesting feedback on its proposals to amend Annex I in this context. However, the Commission's proposed revisions as outlined in this paper are restricted to Part IV of the Annex.

For the reasons outlined above, Novozymes Biopharma believes that changes to the EU master file system are intrinsically linked with accommodating ATMPs and therefore that it is critically important to address these related issues in the upcoming Annex I revision. We strongly feel that this provides the window of opportunity to review the sections governing master files and consider our proposals as discussed in earlier communications, most recently in our contribution to the public consultation on the future of human pharmaceuticals in Europe last year. Indeed, the EC's summary of the outcome of that debate acknowledges the need for a suitable EU MF system for novel excipients to harmonize European and other markets as an issue. Therefore, we respectfully request that the Commission builds this aspect into their current review of Annex I in line with the ongoing consultation process by extending the forthcoming revision to other relevant sections of Annex I, e.g. Parts I and III, to satisfy the urgent need for a suitable regulatory system for novel excipients and biological/biotechnological substances.

As expressed beforehand, we would be most willing to meet with you and your colleagues in Brussels to discuss this matter further if it would be helpful.

Yours sincerely,

KADenton.

Mrs Kate Denton

Regulatory Affairs Manager

[1] Letter from Dr Martin Terberger to Mrs Kate Denton dated 17 October 2006 regarding Master File and biological substances and subsequent emails between Mrs Kate Denton and Mr Nicolas Rossignol dated 4 and 14 December 2006 and 19 and 27 June 2007