14/15 Belgrave Square London SW1X 8PS Telephone: +44 20 7565 7199 Facsimile: +44 20 7565 7191
E-mail: cabouzeid@bioindustry.org Web: http://www.bioindustry.org

Nicolas Rossignol
European Commission
DG Enterprise & Industry
Pharmaceuticals Unit F2
45 Avenue d'Auderghem
B-1049 Brussels
Belgium

10 June 2008

Dear Mr Rossignol,

**BIA response to the European Commission's public consultation paper: Proposals to amend Annex I to Directive 2001/83/EC as regards advanced therapy medicinal products**

The BioIndustry Association (BIA) welcomes the opportunity to comment on the European Commission's proposals to revise Part IV, Annex I to Directive 2001/83/EC so as to adapt it to the specificities of advanced therapy medicinal products.

The BIA is the trade association for innovative bioscience companies in the UK. We represent over 300 members, the majority of which are involved in realising the human health benefits that bioscience promises.

The BIA fully supports the Advanced Therapies Regulation which will enable patients' access to ground-breaking new therapies and strengthen the biotechnology sector in Europe. It provides the long-awaited harmonised regulatory framework for the authorisation and pharmacovigilance of all advanced therapy products comprising gene therapy, cell therapy and tissue-engineered products. We welcome the incentives which are immensely important in stimulating development of such products by companies, which are predominantly small and medium-sized enterprises.

Given that this is an emerging technology area, the technical requirements for assessing safety, quality and efficacy ought to be sufficiently flexible to enable the technology to evolve.

Overall the BIA welcomes the proposals in the consultation paper. We support a risk-based approach for the development, characterisation and testing of advanced therapy medicinal products. We believe that the type and nature of scientific studies ought to take full account of the product characteristics and the underlying mode of action of the advanced therapy medicinal product in question. This is to ensure that only relevant non-clinical and clinical studies are conducted to elucidate the safety and efficacy profile of a specific product.

We provide below our detailed comments on the proposals under the headings used in the consultation paper.

**2.3 Technical requirements regarding Module 3 (Quality data)**

2.3.2 Specific requirements for gene therapy medicinal products

***1.*** *The finished medicinal product consists of nucleic acid sequence(s) or genetically modified organisms or virus(es) formulated in their final immediate container for the intended medical use.*

**Comment:** Clarification is required as to whether the following products should be classified as finished medicinal products as they are often not stored in the container intended for medical use:
(i) those requiring transfer from a long-term storage container to a receptacle to allow product delivery to patients; or
(ii) they are combined with another investigational product before use (e.g. within a hospital pharmacy);
and whether these steps constitute extra processing and therefore would require QP release.

***2.*** *The finished medicinal product consists of genetically modified cells formulated in the final immediate container for the intended medical use.*

**Comment:** As above.

2.3.3 Specific requirements for somatic cell therapy medicinal products and tissue engineered products

**General comment:** Clarification is sought as to when GMP is to be applied in the generation of a cell bank. For example, would GMP apply for the entire cell bank generation, or would controlled procedures such as those detailed in Directive 2004/23/EC be sufficient during the initial tissue outgrowth stages that may be required to generate a pre-cell bank stock.

Clarification is also sought on the status of cell stocks generated within a controlled but unlicensed GMP facility following procedures described in Directive 2004/23/EC. It is proposed that such stocks should be considered suitable for the production of cell banks that would be used to generate medicinal products.

***1.*** *The finished medicinal product consists of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.*

**Comment:** As above under section 2.3.2.

***2.*** *The active substance is composed of the manipulated or engineered cells and/or tissues. Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin.*

**Comment:** Please define what constitutes an “integral part”.

***6.*** *(a) Starting materials*
*(i) If non-healthy cells or tissues are used as starting materials, their use shall be justified.*

**Comment:** Please clarify what is meant by “non-healthy cells or tissues”.

*(iii) The potential variability introduced through the starting material (e.g. variability of donor population such as age, characteristics of cells) shall be addressed insofar as manufacturing process, validation, characterisation, control, stability are concerned, both for the active substance and the finished product.*

**Comment:** Unlike biopharmaceutical products in which specific molecules are purified (e.g. proteins) and hence the product controlled, a cell-based product is not ordinarily highly purified, nor is the mode of action elicited through a single response pathway. As such, it is expected that some level of inherent variability will always remain for a cell-based product since cells are responsive to their environment and therefore variable.

Relevant and appropriate controls will be employed where possible in order to limit the potential variability. However; it is the cells’ ability to respond that provides the function of the product and some variability must be expected and accounted for when defining product acceptance criteria.

Acceptability of the cells within a particular product system should be managed through adequate and relevant in-process testing, end product and, where appropriate, one-off testing to demonstrate the required product characteristics. Test requirements for each product should be assessed and defined on a case-by-case basis using a risk-based approach.

***6.*** *(c) Characterisation and control strategy*
*(i) Relevant information on the characterisation of the cell population or cell mixture in terms of identity, purity (i.e. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumorigenicity and suitability for the intended medicinal use should be provided, unless justified.*

**Comment:** We would welcome guidance on potency assays for tissue engineered products.

*(ii) Qualitative and quantitative information on product- and process-related impurities as well as on any material capable of introducing degradation products during production shall be provided.*

**Comment:** It would not be technically or economically feasible nor would it be relevant to provide qualitative and quantitative information on all materials capable of introducing degradation products during production.

For example, viable cells within the products metabolise - a cellular function essential for an efficacious product. These metabolites may be considered as degradation products. However, it is not relevant or feasible to define in detail such products. The requirement to describe degradation products must be assessed and defined on a case-by-case basis according to risk, depending on the safety implications and overall product system.

*(iv) If biologically active molecules are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised, unless justified.*

**Comment:** Cell-based therapies contain innumerable different biologically active molecules (as cells per se are comprised of and excrete such molecules). Assessment of all biologically active molecules would not be technically or economically feasible. While such

testing is suited to biopharmaceutical products (one protein is expressed for a specific target), this is not appropriate for cell-based products.

It would be more appropriate to assess the behaviour/interactions of components of the product on a case-by-case basis by applying a risk-based approach. Additionally, specific surrogate markers may be chosen to help demonstrate product functionality.

*(v) Where a 3-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products.*

**Comment:** The extent of such characterisation should be assessed on a case-by-case basis taking a risk-based approach. It should be acknowledged that current technical limitations also influence the information that can be provided.

It is agreed that scaffolds should be included in the characterisation of the product with regard to composition and quantification of composition. However, we believe that it may not always be possible to undertake microscopic characterisation of scaffolds. Other physical/mechanical properties such as tensile strength may be more appropriate and relevant.

***6.*** *(d) Excipients*
*(i) Conventional excipients shall also be characterised with respect to their combination with cells.*

**Comment:** It would be helpful to clarify the extent of the characterisation expected.

*(ii) Matrices, scaffolds, devices, biomaterials or biomolecules which are not an integral part of the active substance, shall be considered excipients of the finished product.*

**Comment:** It would be helpful to clarify this statement. Classification as excipients may not always be appropriate.

***6.*** *(f) Reference materials*
*(i) A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised, unless justified.*

**Comment:** It may be extremely difficult to generate a stable, specific standard for both allogeneic and autologous products. It is our view that suitability and acceptability of the product/materials must be built into the process and, when required, verified with appropriate one-off *in vitro* comparability studies.

**2.4 Technical requirements regarding Module 4 (Non-clinical data)**

2.4.1 General requirements for advanced therapy medicinal products

***2.*** *The rationale for the non-clinical development should be based on the above mentioned risk analysis and discussed/justified in the Nonclinical overview.*

**Comment:** We strongly agree that a risk analysis should be undertaken to determine the need for pre-clinical studies to be conducted due to the limitations presented when using animal or other non-clinical models. In many instances, data of limited value can be obtained

from animal models and such studies are not always predictive of the clinical situation. Relevance of non-clinical data should be considered.

2.4.3 Specific requirements for somatic cell therapy medicinal products and tissue engineered products

***1.*** *Pharmacology*
*(a) The primary pharmacological studies should be adequate to demonstrate the proof of principle. The desired interaction of the applied cells with the non-cellular structural component(s) of the product and the interaction of the cell-based products with the surrounding tissue should be studied.*

**Comment:** Clarification is required regarding the type(s) of studies that are contemplated to assess interaction of cell-based products with recipient tissue. Furthermore, the interaction studies are only justified if they are specifically designed to address the underlying safety of the product following administration or implantation.

*(b) The amount of product needed to achieve the desired effect/the effective dose, and where appropriate, the frequency of dosing should be determined.*

**Comment:** For some advanced therapy products it is not appropriate or relevant to define product dose and therefore frequency of dosing as ordinarily done for pharmaceutical products. Restrictions on product use should be assessed on a case-by-case basis according to risk. Furthermore, this may be technically challenging.

*(c) Secondary pharmacological studies should be considered to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product and tissue engineered product or of additional substances. Biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.*

**Comment:** These studies may not be feasible for cell-based products which contain innumerable different biologically active molecules. It would be more appropriate to assess the interactions of components of the product generally.

Specific biologically active molecules may require further assessment. However this requirement must be applied on a case-by-case basis using a risk-based approach.

***2.*** *Pharmacokinetics*
*(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules, shall be studied.*

**Comment:** Cell-based products are biologically active and designed to be capable of responding to the environment in which they are placed. As such the cells illicit the required response to treat, prevent or diagnose disease or for regenerating, repairing or replacing tissue.

As previously discussed, it would not be technically or economically feasible to assess all biologically active molecules that might be produced, particularly with regard to distribution, duration and amount of expression. It is more appropriate to assess the product as a whole

for aspects that are relevant, which would be determined on a case-by-case basis using a risk-based approach.

***3.*** *Toxicology*
*(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product.*

**Comment:** Clarification is required regarding the expected duration of observations. Furthermore, we believe that the length of follow up must take account of the product characteristics and the likely associated risks. Extended follow up may not be required or relevant.

*(d) Potential immunogenic and immunotoxic effects should be studied.*

**Comment:** As above under section 2.4.1.

**2.5 Technical requirements regarding Module 5 (Clinical data)**

2.5.1 General requirements for advanced therapy medicinal products

***3.*** *Due to the nature of advanced therapy medicinal products, their manufacturing process might change during clinical development. Additional studies to demonstrate comparability might be needed.*

**Comment:** Clarification is required regarding the type of studies referred to in this statement. We believe that ordinarily *in vitro* studies might adequately demonstrate comparability. *In vivo* studies should be carried out in exceptional circumstances where the *in vitro* testing system is unlikely to be predictive of the *in vivo* situation.

***4.*** *Dose selection and schedule of use should be defined by dose-finding studies, unless otherwise justified.*

**Comment:** For some advanced therapy products it is not appropriate or relevant to define product dose and therefore frequency of dosing as ordinarily done for pharmaceutical products. Restrictions on product use should be assessed on a case-by-case basis according to risk. Furthermore, such assessment may be technically challenging.

***6.*** *Proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions evidence of long term efficacy may be required. The strategy to evaluate long term efficacy should be provided.*

**Comment:** The term “long term efficacy” should be clearly defined. Furthermore, the need for long term efficacy must be assessed on a case-by-case basis.

2.5.3 Specific requirements for somatic cell therapy medicinal products

***2.*** *The biodistribution, persistence and long term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development, as appropriate.*

**Comment:** Biodistribution studies may not be feasible for such products. The need should be assessed on a case-by-case basis taking account of the product characteristics.

***3.*** *Safety studies shall address aspects, such as:*
*- distribution and engrafting following administration;*
*- ectopic engraftment;*
*- oncogenic transformation and cell/tissue lineage fidelity.*

**Comment:** The studies listed may not be required if they are not relevant to the safety assessment of the product, taking account of the product characteristics, underlying mode of action and the mode of administration.

2.5.4 Specific requirements for tissue engineered products

***1.*** *Conventional pharmacokinetic studies might not be relevant for tissue engineered products. However, the biodistribution, persistence and degradation of the tissue engineered product components should be addressed during the clinical development, as appropriate.*

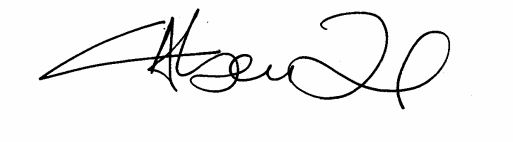
**Comment:** As above re “biodistribution” for somatic cell therapy products.

***3.*** *Safety studies shall address aspects, such as:*
*- distribution and engrafting following administration;*
*- ectopic engraftment;*
*- oncogenic transformation and cell/tissue lineage fidelity.*

**Comment:** As above re “safety studies” for somatic cell therapy products.

Thank you for considering our comments. We are of course pleased to discuss any of them with you in more detail and we look forward to continue working with the Commission during the implementation stages of the Advanced Therapies Regulation.

Yours sincerely,



**Dr Christiane Abouzeid**
BIA Regulatory Affairs Manager