Response by the North East England Stem Cell Institute (NESCI)

To the PUBLIC CONSULTATION PAPER:

Implementation of the 'Advanced Therapies' Regulation (EC) No 1394/2007

Proposals to amend Annex I to Directive 2001/83/Ec as regards

Advanced Therapy Medicinal Products

About NESCI

The North-East England Stem Cell Institute (NESCI) is a collaborative organisation comprising Durham University, Newcastle University, the Newcastle Upon Tyne Hospitals Foundation NHS Trust and other partners.

The Institute draws together a unique interdisciplinary collaboration to convert stem cell research and technologies into cost effective, ethically robust 21st century health solutions to ameliorate degenerative diseases, the effects of ageing and serious injury. To achieve this goal, NESCI supports world-class research on adult and embryonic stem cells, in basic science and in clinical use. More than 120 scientist in over 30 research groups are based at NESCI, and have forged active scientific, educational and commercial links with thousands of collaborators in the region and internationally. The Institute also trains a new generation of basic science and health professionals, hosts stem cell researchers from outside the UK as part of an international consortium for stem cell research, fosters the emergence of new healthcare companies in the North East of England and provides transparent access for public engagement and public information.

A further function of NESCI is to work proactively with policy makers and regulatory authorities to ensure that scientific developments and scientific realities are accurately understood and that emerging development in stem cell science are regulated in a manner that addresses the complexities in science, innovation and ethics in this field.

In this capacity, we are responding to the public consultation.

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Introductory Remarks

NESCI welcomes the opportunity to respond to the consultation.

Whereas the following comments represent the official position of the Institute, no inferences should be drawn as to the views of any particular scientist associated or collaborating with NESCI.

The position reflected in these comments is liable to further refinement and amendments. The Commission and other readers are kindly requested to enquire about an updated statement when considering this response later than 90 days after the issue date of June 10th 2008.

The response may be used and distributed freely as long as the content is not changed and attribution is given to NESCI.

If on any point in the response, the position of NESCI is not sufficiently clear, readers are invited to contact NESCI for clarification. We also invite further questions, feedback and other comments.

All comments are in reference to the version of the public consultation paper dated: 8 April 2008

The following response is divided into general comments and specific comments.

A. General Comments

1) We welcome the fact that the Regulations aim to establish a harmonised scientific evaluation for Advanced Therapy Medicinal Products to guarantee an even level of safety and efficacy throughout the European Union. It is desirable that a centralised procedure should guarantee a uniformly high level of expertise and avoid variations between Member States.

2) However, this Regulation does not seek to address different national ethical approaches for which there is no EU competence. Issues such as the use of embryonic stem cell research, and the products that may be derived from this research, and similar considerations that go beyond the establishment of common standards on safety and efficacy must be left up to Member States, and ultimately, to the discretion of regulators, innovators, physicians, patients and their families.

3) We welcome the recognition by the regulators that due to the specific nature of advanced therapy medicinal products, a risk-based approach can be applied to determine the extent of characterisation in terms of Quality, Nonclinical and Clinical data to be included in the marketing authorisation application. It must be unequivocally clear that a 'precautionary' approach is not appropriate in situations where patients seek therapies to avert or mitigate serious or life-threatening conditions.

A. General Comments (continued)

4) It is implicitly clear that all discussions on "Advanced Therapies" concern regimes of scientific, clinical and commercial conduct that to not fit the mould of existing medicines.

   a) It is crucial that standards and practices in other fields are not imported and imposed to ATMP without a careful assessment whether these standards are appropriate and effective.

   b) Innovators in this field are predominantly academic or academic spin-out ventures, often with limited experience of medicines regulation and very limited financial capital. It is crucial that regulations and codes of practice are shaped in a way that allow regulators to work constructively with researchers and clinicians towards a shared sense of purpose: to accomplish a transition of science to therapy swiftly, safely and responsibly.

   c) Regulators must be aware that in an emerging field even 'little things' such as inability to access appropriate guidance or rigid application of inappropriate standards can have an instant 'ripple' effect on the entire fledgling community, and can inadvertently stifle all innovation in a particular area of ATMP.

5) Cell therapy departs from a focus on 'simple' ligand-receptor interactions, but often also does not present a product the effect of which can be defined purely by its presence (such as whole-organ transplantation). As such both safety and functionality of the product cannot be assessed straightforwardly in vitro.

   a) Cell populations in many therapies are necessarily heterogeneous. The search for optimal purification protocols which is applicable for other contexts may not be appropriate for ATMP.

   b) Cells are very complex entities that react very sensitively to a variety of stimuli, some of which cannot be replicated in vitro, and some others which can only occur as an in vitro artefact. It is therefore not always possible to draw inferences from in vitro data to the potential behaviour of cells in vivo or in a particular patient.

   c) Stem cells are often used precisely for their ability to differentiate into a variety of cell types and to engender changes in surrounding tissue. Thus any isolated assessment of proliferation profile and reactivity will always be insufficient. Almost all cells harbour a potential to proliferate in unexpected ways. Where neoplasia and oncogenicity are a theoretical concern, it is necessary to validate these applications using animal testing and ultimately in clinical trials. In situations where ATMP represent the only option to halt or mitigate the progression of a serious life threatening condition, lingering concerns about the long-term potential of neoplasia must be weighted carefully against a patients chances of survival without the intervention.

B. Specific Comments

The sections below correspond to the outline preliminary proposals to replace the current Part IV of Annex I to Directive 2001/83/EC.

We recognize that the purpose of the consultation paper is not to outline detailed legal amendments, but to provide a basis for discussion on key elements for revision of this Annex. We respond on this basis, but also point out where the specific wording of the consultation document may be of interest if it was transposed verbatim into law.

We have no comments to make on specific sections that are not listed below. Our general comments above apply throughout.

Comments on the consultation, section 2.2.1

Gene therapy products according to the definition given in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC):

"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 gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell."

In contrast, the proposed definition would qualify any therapeutic antisense oligonucleotide, ribozyme and siRNA as a gene therapy medicinal product. This would also affect substances which are either already in clinical trials or are already in clinical use. None of these synthetic oligonucleotides has the capacity to integrate into the genome nor to lead to any other permanent modification of the genome.

It is troubling that in later references (e.g. 2.4.2-3(g)) the draft proposals recognise the prospect of gene therapy medicinal products which are "not expected to be capable of integration" and where "nucleic acid sequences will not enter into the cell nucleus".

A number of therapeutics may be nucleic acid-based but nonetheless be more typical of 'traditional' pharmaceuticals in pharmacology. The function of e.g. siRNA does not require their transcription or translation. The effect of antisense therapeutics is completely dependent on their temporal presence in cells and their activity wanes as they are metabolized by nucleases and cleared from the body. This is in contrast to true gene therapy medicinal products that can become integrated into the genome and produce permanent changes to the genome or be shed or self-replicate.

In summary: A more appropriate definition of gene therapy medicinal products is urgently required. Such a definition should account for why gene therapy products are treated differently from other medicinal products from a perspective of safety and efficacy.

B. Specific Comments (continued)

Comments on the consultation, section 2.3.2- 5(f)

The wording of this provisions may confuse for a number of reasons:

- The word 'transduction' is not otherwise defined. Is this meant to include all ways of effecting a genetic change listed in 2.3.2 -1 ?
- Are 'pre transduction' cells to be tested each time before and after freezing? This would seem an unwarranted and unnecessary burden of limited utility for clinical safety. What about situations where long-established cell lines are 'starting materials'?
- The expression "phenotypic characteristics" is not otherwise defined. Is this test meant to elucidate merely e.g. and intact morphology or are detailed biochemical properties required?
- The ratio behind this provision is not entirely clear. Whereas in-process testing and validation of quality at clinically meaningful points is certainly a consideration in cGMP, such tests should be conducted in a context where they are useful to ensure the safety and quality of the ATMP, not at rigidly defined process stages.

Comments on the consultation, section 2.3.3- 2

The wording of this provision leaves room for interpretation that may lead to inappropriate regulatory standards:

- Cells are living entities that require a range of provisions to be kept in a viable state. Thus, any one of the substances listed in these provisions could be considered as being 'combined as an integral part'.
- Are "biomolecules" and "other components" which have been digested by the cell considered to be "combined as an integral part" and thus as "starting materials"?

Comments on the consultation, section 2.3.3- 5

This provision runs the risk of introducing unintended or inappropriate requirements by the backdoor. In reference to the general remarks above, it would be preferable to approach ATMP as entirely sui generis without generic reference to standards in other fields.

Comments on the consultation, section 2.3.3- 6(a)(i)

The provision for 'non healthy' cells is difficult to place. E.g. is an aged cell/tissue 'non healthy' compared to a younger cell/tissue? It would seem extremely unlikely that 'diseased cells' will be used frivolously without scientific or clinical justification, and those cases would be flagged up in the general regulatory assessment. At best this provision may require unnecessary 'red tape' in formulating a justification.

Comments on the consultation, section 2.3.3- 6(a)(ii)

Traceability and 'batch record' provisions should allow for pooled or 'rollover' cell bank establishments.

B. Specific Comments (continued)

Comments on the consultation, section 2.3.3- 6(a)(iii)

Regulations and Regulators must recognise that variability as such is not necessarily a detriment to cGMP in ATMP. Minimising variability may seem desirable from the position of regulatory control, yet not only may it not be achievable in some ATMP applications, it may even be detrimental by narrowing the scope for patient-specific therapeutic uses.

Comments on the consultation, section 2.3.3- 6(a)(iv)

Regulations and Regulators already recognise that the use of animal components as such is not necessarily a detriment to cGMP in medicinal products. This should be affirmed in the context of ATMP.

Comments on the consultation, section 2.3.3- 6(b)(i)

The list of 'purity' factors given is not exhaustive from a safety perspective and may not be appropriate for certain types of ATMP. The wording "i.e." should be replaced by "e.g."

Comments on the consultation, section 2.3.3- 6(b)(ii)

- The use of production batch records is a cornerstone in many other types of medicinal product. As a principle, it is desirable to use production batch records in many types of ATMP. However, the system may not be suitable for certain types of ATMP. For example, some types of tissue engineered ATMP may be extremely complex products that are grown a varying times and stages using individually adjusted formulations of starting materials; some types of cell therapy ATMP may be drawn from pooled or 'rollover' resource banks; etc.
- The requirement to validate functional integrity at the moment of application may put an excessive burden on clinical sites. If the functional integrity of the ATMP can be demonstrated and warranted during transport and handling, further validation at the moment of application may lead to excessive delays and costs and may even compromise the ATMP.
- We recommend that the provision should include "unless this is demonstrably impractical" or words to that effect.

Comments on the consultation, section 2.3.3- 6(c)(ii)

It would be helpful if the Commission could give examples and elaborate on what are considered "degradation products" in the context of ATMP.

Comments on the consultation, section 2.3.3- 6(c)(iii)

This provision is a welcome recognition of the fact that certain requirements are not suitable for ATMP.

Comments on the consultation, section 2.3.3- 6(d)

- The provision has to be considered in relation to current frameworks for excipients. Common Excipients are widely used pharmaceutically inactive substances, which are appropriately evaluated for safety using available standards and intentionally included in a drug delivery

B. Specific Comments (continued)

system. Against this background, it may be good practice to treat novel excipients under a regime of special regulatory scrutiny in certain established fields. In ATMP however, almost all reagents are novel at this stage.

- What does the wording "for the first time" indicate? First use in a documented regulatory context, in scientific publication, in common usage?
- What does the terminology of "with cells" signify in this context? Does this mean any type of cell, the specific celltype that is crucial for the function of the ATMP, or any new variation in phenotype that cells in the ATMP undergo throughout its manufacture?
- In the wording of "in combination with" and the provisions of paragraph (ii), fail to set clear parameters of what constitutes an excipient.
- In summary, section 2.3.3- requires thorough revision. In most ATMP a moratorium on regulatory assessment of excipients would be indicated.

Comments on the consultation, section 2.3.4-2(b)

Regulations should account for the possibility that Annexe 1 of Directive 93/42/EEC or Directive 90/385/EEC respectively may not be fully appropriate for combined ATMP. For example the requirement for sterile packaging in may not be applicable to certain products.

Comments on the consultation, section 2.4.1-1

It is to be welcomed that the provisions recognise that conventional requirements for pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of the products.

Comments on the consultation, section 2.4.1-2

Many ATMP strategies will be targeted in very precise ways to very specific disease situations. Any generic or prescriptive approaches to what is a suitable model for non-clinical development are likely to be inappropriate for ATMP. Regulators should be encouraged to work proactively with the scientific community to establish which models are likely to yield the most suitable data at an sustainable cost.

Comments on the consultation, section 2.4.1-3

By inserting the word 'relevant' prior to "additional substances" regulators could demonstrate an awareness of regard to the principles of best regulatory practice (including the principles under which regulatory activities should be transparent, accountable, proportionate, consistent and targeted only at cases in which action is needed.

Comments on the consultation, section 2.4.2-3(g)

See our comments on section 2.1 (above)

B. Specific Comments (continued)

Comments on the consultation, section 2.4.2-2(a)

We welcome the wording of "as appropriate" but we would like to ensure that this is clearly linked with the list of the parameters listed rather than with the wording of "over time". We would therefore suggest the following re-wording:

"Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion are usually not relevant. However, where appropriate, parameters such as viability, longevity, distribution, growth, differentiation and migration should be investigated over time."

Comments on the consultation, section 2.4.2-2(b)

This requirement could be interpreted as putting an unwarranted and unobtainable burden on complex ATMP. As an analogy: in organ transplantation, the 'biomolecules' emitted by the whole organ are not generally studied let alone exhaustively understood. The requirements of this provision could be seen to depart from the risk-based approach that the regulations posit. The words "as appropriate" should be added.

Comments on the consultation, section 2.4.2-3(b)

It is unfortunate that product lifespan is the only listed factor that influences the duration of safety observations. A multitude of other factors are of relevance.

Comments on the consultation, section 2.5.1

In general we feel that the provision in this section are worded appropriately. Given the importance of provision 2.5.1(7) it may be useful to re-iterate it in the introductions. Also, on the basis of that provision, it would be desirable to establish further guidance on combined ATMP.

Comments on the consultation, section 2.5.3-1

This wording focuses on somatic cell therapy ATMP where the "mode of action" is linked to a specific biomolecule. This is the only instance where "mode of action" is used, usually the regulations refer to "function". Moreover, the provision is ambiguous about those somatic cell therapy ATMP where some active biomolecules have been identified as contributing to the therapeutic function, but only in conjunction with other factors that are not biomolecular or have not been fully identified. Modelled on other provisions in this section, the following wording would be preferable:

"Conventional pharmacokinetic studies might not be relevant for some somatic cell therapy medicinal products. However, for somatic cell therapy medicinal products where whose function is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules shall be addressed during the clinical development, as appropriate."

In summary, we believe that the regulatory provisions can make a very positive contribution towards harmonisation of regulatory regimes in advanced therapies. However at this stage in the drafting process, policy makers need to work proactively with all stakeholders to identify areas where careless drafting or rigid adherence to inappropriate standards might damage the prospect of transitioning advanced therapies from science to therapy in a ethical and sustainable manner.

Submission ends here

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