Response by the North-East England Stem Cell Institute (NESCI)
on the document for public consultation
by
European Commission, DG Enterprise & Industry, Unit F2 'Pharmaceuticals'
on
DRAFT DETAILED GUIDELINE ON GOOD CLINICAL PRACTICE SPECIFIC TO 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 scientists 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 frameworks 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 draft for public consultation.

Please note:

- 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. Readers are kindly requested to enquire about an updated statement when considering this response later than 90 days after the issue date of October 15th 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.

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Comments

General Comments

Advanced Therapy Medicinal Products are at the vanguard of medical research and development, crossing established conceptual, disciplinary, and regulatory developments. While great hopes are associated with this generation of medicinal products it is clear that the successful development of such therapies is contingent on a system of innovation governance where laws, regulations, and official communications can have an immediate impact on feasibility expectations and financial investment in the entire field. The economics, health risks and benefits of these very diverse products are still largely unexplored. Thus, regulators in this area have a great responsibility: a single adverse incident can destroy public confidence and set the entire sector back years, while a single ill-advised regulatory prohibition could stifle development in a whole field.

The continual consultation of regulators with the stakeholder community is therefore very welcome.

Advanced Therapy Medicinal Products Exceptionalism

It is important in this context to remain consistently clear why ATMP and ATIMP are deemed to require a separate or additional regulatory regime, and to minimise inconsistencies that cannot be justified on the basis of risk.

As an example, the guidelines state that "Where an ATIMP contains or consists of tissues or cells, other actors than the sponsor and the investigator need to be considered" and proceeds to list other notable contributors. However, 'other actors' than the sponsor and the investigator are always a factor in medical innovation, in any product class. The assessment regarding which third parties are subject to regulatory scrutiny should not be product but risk-based, and should be consistent within an equal risk category across product types.

The focus on good clinical practice

The concept of good clinical practice is inherently international. It aims at establishing common standards in the context of clinical trials. As such, any deviations from the ICH Harmonised Tripartite Guideline and similar international documents must be carefully considered. Especially in the light of other provisions on ATMP (e.g. the pending amendments to Annex I to Directive 2001/83/EC, the draft EMEA guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products) it is appropriate for the Commission to outline minimum provisions and to defer to other documentation. Redundancy is not a virtue where it leads to potential inconsistencies between guidelines and to a perceived inflation of "paperwork" that daunts clinicians unnecessarily.

We welcome the fact that the document simply references 2005/28/EC and CPMP/ICH/135/95 without adding many further specifications regarding, inter alia, the investigators brochure, the clinical protocol, ethics quality control etc. However, this approach does bring a particular emphasis to the points that the document selectively focuses on. As discussed in the following section, it is unclear whether a particular focus on traceability rather than any other aspect of GCP is always appropriate for ATIMP.

Comments on the emphasis on traceability

Traceability of the donor: It is now an established principle in medical innovation and in routine use to aim for complete batch traceability. This gives better information in identifying sources of risk, analysing adverse incidents and constructing the safety profile of the medicinal product. Traceability features prominently in Regulation 1394/2007. However, traceability is not a static concept. In GCP, traceability is not usually the focus: words relating to "tracing" only occur once in 2005/28/EC (and only to specify that "any alteration to records shall be traceable" Art.20), and are not mentioned once in CPMP/ICH/135/95. This calls into question whether the emphasis on traceability in this GCP-focused document is well placed. It is important to remember that traceability is a safety instrument, not an aim in itself. In some ATIMPs, there may not be a clear rationale for establishing traceability 'back to' an original donor.

For example: in therapies based on embryonic stem cells, it may not be reasonable to maintain traceability to the donors of the gametes; in products relying on established cell lines –whether human or animal– with a well-defined profile, traceability to the original donor serves no useful purpose; in products linked to 'pooled' cell banks, donor traceability may be inherently unachievable, etc.

Traceability of the subject: It is clear that some ATIMP are intended to persist for a long time in the recipient. It is important that such patients are never abandoned, but is also important that they are not stigmatised, burdened unduly, or exposed to perpetual infringements of their privacy.

Recital 22 of Regulation 1394/2007 provides that "*The traceability system should also respect the provisions laid down in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data*". It is clear that a thirty year record keeping requirement applies in this area, but not clear whether there should be a dynamic, perpetual link to medical records. In particular for unpaid volunteers, the spectre of prolonged regulatory surveillance may lead to an undermining of the principles of altruistic procurement that the regulations espouse.

Traceability in the document: There are instances where the consultation document uses 'traceability' in a context that might be rendered clearer.

- In s.2.3.2.1 the document uses the phrases "the integrity of the traceability" and "that the traceability of the ATIMP can be linked". As one would not expect that any additional concepts are eluded to here, it might be easier to state: "the traceability" and "that the ATIMP can be linked" respectively.
- In s.2.5 the phrase "arrangements for traceability" is used in the first and the fifth item. Here also, unless this means to imply some further concepts (which should then be more clearly explained), it may be helpful to delete one or the other.
- In s.2.10.1 and s.2.10.2 the phrase is repeated that "Each party should hold the necessary information linking the donor information to the ATIMP and the clinical trial subject and vice versa". However, it is clear at least from s.2.10.2 that is not necessary (and indeed it may not be desirable) that each party holds the entirety of this information in one place. In fact, s.2.10.3 points out that comprehensive consolidation is only anticipated after completion or termination of the trial. We assume that the intention is for each part to hold the necessary information to maintain, if linked, an unbroken chain of traceability. It may be helpful to clarify the guidance accordingly.

Other Comments

Reference to the environment

Good Clinical Practice has an accepted remit in the clinical community as relating to the protection of trial subjects and to generating and reporting credible and accurate results. GCP in Advanced Therapy Products should not provide a 'backdoor' to introduce other interests that may be noteworthy in themselves but would dilute the focus on GCP in this document.

Therefore requirements and references relating to "the environment" (in 2.6, 2.7 and 2.9) and to "shedding" (in 2.5 and 2.8) may be inappropriate where they concern matters outside those reasonably in the sphere of a clinical trial (e.g. shedding may be a GCP concern where it could affect other patients or relatives of the subject, but it would not be a GCP concern where its long term effects on the biosphere are considered – this should be raised at a different forum).

Exemptions

Article 5.1 of Directive 2001/83/EC provides that "*a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility*".

Article 3.7 (as amended by 28.2 of Regulation (EC) No 1394/2007) states "*Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.*"

In this context, it would not be suitable to supply periodic follow-up safety and efficacy reports for products that are produced on a non routine basis. It may be more appropriate to monitor such interventions in the context of a professional obligation for clinicians.

"Type of donation"

The suggested "minimal dataset" in section 2.3.3 contains the item "Type of donation". It is rather unclear what is expected here. The items given are listed as "examples" with no indication whether this is a minimal list, according to which criteria the list should be substituted or expanded, and how these 'types' apply in products that span or combine more than one category.

Comments section ends here

We thank the Commission for the opportunity to respond to this consultation.

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