First-in-human clinical studies: challenges for ATMPs

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Abstract

This article discusses some of the issues associated with proceeding to a first-in-human (FIH) study in the EU with an investigational advanced therapy medicinal product (ATMP). As many readers will be aware, ATMPs are a relatively new class of medicinal products, comprising gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products[1] (see Box for regulatory definitions). Some general aspects that may differ from other biological/biotechnological medicinal products are highlighted. The article does not seek to discuss every possibility that may arise with such a diverse range of therapies, but instead aims to identify the general principles for consideration before first administration to a human subject.

Legislation and guidance

Clinical trials conducted in the EU using advanced therapy medicinal products (ATMPs) as investigational medicinal products (IMPs) are currently regulated under the Clinical Trials Directive[2] and require national clinical trial applications (CTAs). For gene therapy (GT), somatic cell therapy (SCT), tissue engineered products (TEP) and all medicinal products containing genetically modified organisms, the time limit for the Ethics Committee opinion and authorisation by a national competent authority is currently a maximum of 90 days (*cf* 60 days for other IMPs) after receipt of a valid application, although with justification this can be extended to 180 days.[2] In the case of cell therapies consisting of xenogeneic cells there is no maximum time limit for the assessment of the CTA. A specific authorisation is also required for the use of genetically modified organisms but this requirement will not be covered further in this article.

The European Medicines Agency (EMA) guideline on FIH studies[3] specifically excludes gene and cell therapy medicinal products; however, the general approach to first exposure of a human subject should be followed, with relevant precautions and risk assessments as discussed in the guideline.

General quality considerations

The "Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials"[4] is a recommended starting point for the chemistry, manufacturing and controls (CMC) content of an advanced therapy IMP dossier (IMPD). Although ATMPs are not in scope, the Guideline represents the expectations of regulators regarding biotechnology products and therefore is a valuable reference. Additional considerations for an FIH application and product development generally are included below.

The sourcing of good manufacturing practice (GMP) grade materials for ATMP manufacture may be challenging and a justification for the use of non-GMP materials and a description of their quality control should be provided. Variability in quality and/or composition may be unavoidable for some materials, eg, autologous (patient) tissues or cells, and this should be explained in the context of being "fit for purpose".

Consideration should be given to suitable specification tests for drug substance (DS), drug product (DP) and where relevant, starting materials, and the inclusion of potency assay(s) indicative of (anticipated) mechanism of action (MoA). Where real time release is necessary, the quality control strategy for the real time release testing should be justified and will probably include a combination of tests and controls throughout manufacture and limited product testing, with the inclusion of sterility assurance.

Characterisation of the cells for a cell-containing product over the course of the process is required and there should be sufficient evidence prior to commencing the FIH study to give confidence that the cell phenotype is as expected, and that there is a reasonable degree of consistency in the manufacturing process in terms of the cellular output. The principles of ICH "Q5E Comparability of Biotechnological/Biological Products"[5] should be considered from early development, since it is inevitable that changes will occur during development and therefore comparability of pre- and post-change product will need to be assessed. Data from extended characterisation testing, used to increase product knowledge, should be included in the IMPD. Data generated at this stage of development can be informative regarding the potential impact of planned changes. Useful guidance on characterisation of cells is given in the BSI publication "PAS 93: Characterisation of cells for human application",[6] although this document has no formal status with regulatory agencies.

Finally, the systems which need to be in place to ensure controlled delivery of the final product for administration should be scrutinised and will include traceability of the individual product and its starting, raw and contact materials through to final use. Traceability for the human cells must be consistent with the requirements of the EU Directives on quality and safety of human cells and tissues. Information can be included in IMPD section A1.

A particular issue with many ATMPs is their likely sensitivity to temperature and other conditions. It is therefore advisable, prior to

Regulatory definitions for ATMPs

From Directive 2001/83/EC Annex Part IV

- ***Gene therapy medicinal product*** means a biological medicinal product which has the following characteristics:
  (a) It contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence
  (b) Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

- ***Somatic cell therapy medicinal product*** means a biological medicinal product which has the following characteristics:
  (a) It contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor
  (b) It is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

From Regulation No (EC) 1394/2007

- ***Tissue engineered product*** means a product that:
  - Contains or consists of engineered cells or tissues
  - Is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
- ***Combined advanced therapy medicinal product*** means an advanced therapy medicinal product that fulfils the following conditions:
  - It must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and
  - Its cellular or tissue part must contain viable cells or tissues, or
  - Its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

starting an FIH study, to conduct some studies confirming the ability of proposed transport containers to maintain temperature and any other critical conditions, and to ensure that logistics of transport and receipt at the clinical site are under sufficient control to ensure the viability of the IMP.

Specific quality considerations for SCTs and TEPs

Starting at the beginning of the process, all human cells and tissues for human application (ie, clinical use) must be donated, procured and the donor tested in accordance with the EU Directives on quality and safety of human cells and tissues.[7,8,9] For autologous cells the viral tests specified as a minimum in 2006/17/EC[8] may be sufficient, but for cells for allogeneic use the sponsor should develop a rational programme for extended viral safety testing based on factors such as the location of the donor, their health status, history of high-risk behaviours that could increase the risk of viral disease, history of foreign travel and testing for viruses in relation to the specific tissue/cell type being donated. The principles of ICH Q5A[10] should be applied but for SCT and TEP products it should be kept in mind that the cells become the IMP whereas the guidance in ICH Q5A[10] is designed for cells used as a substrate for manufacture of subsequently purified proteins. Most importantly it is impossible, in most cases, for any kind of viral clearance or inactivation steps to be undertaken. It should not, therefore, be assumed that the guideline will address all issues relevant to the use of the cells themselves. As for any biotechnology-derived medicinal product, viral safety testing and validation of inactivation/clearance steps of other starting materials and reagents must be done before FIH studies commence. Process validation to confirm that the manufacturing process can be performed maintaining aseptic conditions is also necessary.

Cells which are banked for extended storage and culture should be established, documented and characterised for safety and function in line with the principles of ICH Q5D,[11] but for SCTs and TEPs the same caveat applies as for ICH Q5A.[10] Detailed information on population doubling of cells should be kept to support safety (cytogenetic assays, tumourigenicity).

Clear evidence of identity and purity of the cell population should be available for FIH studies. Although it may be possible to start clinical development without a definitive potency assay there should be some evidence of relevant biological functionality. The development of more than one functionality assay is to be encouraged as it improves the sponsor's ability to identify suitable potency assays early on in the clinical development phase, and linking the functional qualities of cells from each study is extremely important to maximise the relevance of the information gained. In the case of products derived from human embryonic stem cells (hESC), a sensitive and specific assay will be necessary to ensure that no undifferentiated hESC are administered because of the risk of teratoma formation associated with the administration of pluripotent stem cells.

In the case of a combined ATMP, the sponsor will need to assess the relevance of any pre-existing data on the device element for use in the IMP. Reference to a CE-mark may be useful although the device's intended purpose may not be relevant for the IMP, for example the manufacturing process for the IMP may subject the device material to conditions of moisture, humidity, etc, not foreseen by the device manufacturer. The general suitability of the device element of a combined ATMP should be demonstrated as part of the manufacturing process development and stability of the IMP, although detailed characterisation of the material may not be necessary at the FIH stage.

A thorough and detailed risk analysis for the cell sourcing, processing, media and other materials, and manufacturing process is of critical importance for SCTs and TEPs because of the inability to conduct sterilisation or inactivation processes on the viable cell-based IMP.

Specific quality considerations for GT products

Gene therapy products are diverse and include direct administration of vector (viral or non-viral) and the use of genetically modified (GM) cells. Some quality considerations are shared between product type, for example, analysis of transgene activity. However, there are also a number of specific considerations dependent on therapy type and method of manufacture. For example, for viral vectors manufactured from cell banks or viral banks, the European Pharmacopoeia (*Ph Eur*)[12] chapters regarding cell substrates for biotechnology products and vaccines should be consulted and bank testing information provided in IMPD Sections S2.3 and A2. For products containing genetically modified cells, the components used to modify the cells are starting materials.[13] These can be described in IMPD section S2.3, for example, using many of the CMC IMPD section headings to create subsections to describe the vector development, characterisation, production and quality control.

Gene therapy guidelines are available on the EMA website, and *Ph Eur* chapter 5.14: "Gene transfer medicinal products for human use",[14] despite its scope for commercial product, is a useful reference regarding quality control considerations for various gene therapy types.

It is important to consider how the active substance(s) and the product-related impurities will be described in the IMPD. This may not be straightforward for GM cell therapies where the specific cell population(s) required for the desired clinical effects may not be self-evident, or it may not even be possible to directly measure these cells. The decision regarding active substance will impact clinical trial design and quality control of the IMP. Time should be spent on a rationale for the chosen approach and the guidance regarding SCTs should also be consulted.

Requirements for autologous therapies

The requirements of Directive 2006/17/EC[8] apply equally to autologous cells as to donated (allogeneic) cells unless the autologous cells are returned to the patient within the same surgical procedure as the one in which they were harvested. This is primarily to inform the manufacturer regarding risks to employees and to the integrity of the manufacturing facility, although in respect of the safety of patients the potential for increased expression of virus as a result of extended processing of the cells, and for inadvertent mix-up or cross-contamination of different patients' cells, should be considered. The directive does not exclude the use of cells to manufacture autologous products for an individual who is virus-positive, but the decision to handle the cells/tissues is one for the manufacturer.

For autologous products, process development work should include some exploration of the extent of variability arising from the donor in properties relevant to the intended biological function of the IMP. If autologous tissues/cells are scarce because of their biological source or difficulty in culturing them, it may be possible to use surrogate tissues for development work provided that a thorough comparison of relevant similarities and differences in function and behaviour, and justification for the use of a different cell/tissue, can be provided.

The extremely time-sensitive nature of many autologous therapies means that conventional approaches to testing and product release may be impossible or impractical. The regulatory authorities are sensitive to these issues and now anticipate that sponsors will require novel approaches to the control strategy. Timing of tests for microbiological quality (sterility, endotoxins and mycoplasma) should be explored during process development, and full use should be made of the rapid detection methods described in the *Ph Eur*. While the IMP may be released on the basis of rapid methods, parallel pharmacopoeial testing is generally expected for post-release confirmation of product microbiological quality. An action plan/procedure should be developed in conjunction with the clinical investigator(s) in the event that positive results are received after the product has been administered to a patient.

Despite the definitions in 2001/83/EC Annex Part IV, it may sometimes be difficult to make a formal distinction between DS and DP, especially for some autologous therapies, so it is important to set out in the IMPD how this distinction is made. For example, the DS for cultured autologous chondrocytes may be considered to be the cells suspended in medium to a specified concentration (cell density), whereas the DP may be the same suspension (the total yield) in a transport vial. Scientific advice should be sought in particularly problematic cases. There may not be time, or even sufficient material, to conduct separate tests on identity, purity and potency on both the DS and the DP, and a justification for this, explaining why the proposed approach is adequate, should be provided.

Nonclinical development – general safety aspects

It is generally recognised that ATMPs present very specific challenges in terms of nonclinical testing, and that a conventional approach, in particular to safety testing, is not appropriate. Because of the huge potential variation in product type and biological activity, a "one size fits all" ATMP development strategy is not justified either. The design of safety and proof-of-concept tests for ATMPs can best be determined via the risk-based approach recommended in the EMA "Guideline on Cell-Based Medicinal Products".[15] The amount and type of data required to proceed to an FIH study will vary considerably between product types (GT, SCT or TEP) as well as according to risks associated with transgene products, cell differentiation status, implantation or integration site and method, secretion of biologically active molecules from implanted cells, intended IMP distribution or localisation, likely duration of persistence and the clinical impact of the indication for which the IMP is proposed.

Investigations regarding the safety of ATMPs raise the challenge of a relevant animal model for the study of vectors with species-specificity and allogeneic and autologous cell therapies. The use of immunocompromised animals, such as nude or SCID mice, may permit some understanding of the hazards from gene therapies, eg, insertional mutagenesis. However, homologous models may provide clearer insight into specific questions. For example, the use of *ex vivo* genetically modified animal host cells to study the tumourigenicity risk from a viral vector in a pertinent disease model.

Consideration should be given to the safety questions which need to be addressed prior to and during clinical development and a model which could provide meaningful results. A well-designed homologous model may assist with knowledge gaps provided that the limitations of the model are understood.

Specific nonclinical considerations for SCTs and TEPs

The EMA has produced a general guideline[15] containing considerable information on nonclinical development from the perspective of the required content for the marketing authorisation application (MAA). Not all of this information is expected at the FIH stage but it gives some clear guidance regarding the relevant issues. The extent to which each aspect should be covered before first administration in humans will depend upon the cell type, extent of processing, anticipated MoA, and the benefit–risk balance for the intended indication.

The tumourigenic potential of cell-based products must be investigated prior to the FIH study and should be performed with cells at the limit of routine cell culturing or beyond. The effects of culture and processing, in particular repeated passaging, need assessment and a safe level of population doubling determined which can be applied to all future process development. The proliferative capacity of the cells and point of senescence should be determined. For banked cells, demonstration of normal karyology is required. Tumourigenicity testing of TEPs should include testing of the final construct, in a suitable animal model that reflects the site of administration as far as possible.

Some data should be provided concerning distribution of the cells following administration, especially in the case of TEPs for which a local MoA is proposed. The distribution, persistence and maintenance of phenotype of administered cells should be assessed to the extent supported by the risk analysis, as should the need for studies of end-organ accumulation, ectopic grafting and unintended *in vivo* transformation.

In the case of combined ATMPs, the device element of the combination should be included in the safety studies for obvious reasons. It is not necessarily sufficient to rely on the existence of a CE mark for the device because this is given in the context of the intended use specified by the device manufacturer. For example, conformity assessment for a topical wound dressing material is unlikely to include implantation studies or studies on compatibility with specific cell types. In any case it cannot be assumed that the device manufacturer would agree to make available any study data to the IMP manufacturer. At this early stage in development of the IMP, the inclusion of the device element in the IMP safety studies and assessment of general toxic effects at the site of administration may well be sufficient, unless a particularly sensitive location of use is intended. Suitability of the device element for its function in the combined ATMP should be investigated, for example support for proliferation of the required cell type, maintenance of structure or degradation within the expected timeframe should be established.

The administration of viable allogeneic cells gives rise to specific challenges in respect of immune response: the prediction of the human immune response to administration of the IMP, and the impact on interpretation of nonclinical safety/proof-of-concept results of using human cells in a non-human model. The use of homologous models may be helpful in avoiding xenogeneic response to human cells, but this in itself may not be predictive of the actual immune consequences of administration of allogeneic cells to humans. The formation of neutralising antibodies may have confounding effects on both the safety and functionality findings of a study. It will probably be necessary to develop a multi-factorial approach to safety testing in which immunologically compromised animals are used for aspects that do not involve immunogenicity assessment of the IMP, because a distinction must be made between the effects of the test animal's immune response to the administration of xenogeneic cells and the likely allogeneic consequences of administering the IMP in humans.

In vitro testing approaches to prediction of immune reactions, such as the mixed lymphocyte reaction, may be helpful. ICH S6 provides some useful guidance in the context of immunogenicity testing, although cell -based therapies are outside of its scope. The FIH IMPD should contain some evidence that immunological risks have been investigated in relevant models and that other safety risks have not been underestimated because of the effect of neutralising antibodies.

Proof-of-concept studies need to be designed with a critical assessment of the suitability of the animal model in terms of its ability to demonstrate the required effect(s). Indications relating to regeneration or repair of structural tissues such as bone or cartilage may require the use of a large load-bearing animal model (eg, sheep, horse) to address biomechanical considerations. Such studies do not lend themselves to formal good laboratory practice (GLP) compliance, so adaptation of the principles of GLP becomes necessary. Long term proof of effect nonclinical studies (>1 year) will ultimately be necessary but may not always be required prior to initiation of an FIH study. In some instances there is no adequate model (for example chronic wounds arising from complex aetiologies) and proof-of-concept may need to be limited to specific pharmacological actions such as proliferation of relevant cell types, formation of functional barrier properties in the repaired wound.

Specific safety considerations for GT products

There are particular concerns for particular types of gene therapy. Replication recombinant viruses (RCV) are a potential concern regarding the spontaneous ability of a viral vector to become self-replicating and potentially pathogenic.[16] In addition the vector/virus could be shed by the patient to generate a potential exposure risk.[16] Information should be provided in the IMPD regarding the concluded risk from RCV and data to support this.

The potential risk of germline alteration and reactivation of latent viruses are also considerations, for example due to undesirable insertional events, and these risks should also be assessed[16] and the conclusion from the assessment provided.

Where homologous models are used for nonclinical studies, but a homologue of the vector/virus is not used, interpretation of results should be cautious since the efficiency and impact of genetic modification of target cells and resulting exposure may not be representative of human exposure. If the disease/genetic background is believed to be an important factor for GT risk, the relevance and applicability of using non-disease material (eg, donor cells) as part of the model should be outlined.

For GM cells, guidance regarding SCTs should also be consulted since concerns as outlined above for SCTs, such as tumourigenic potential, distribution, persistence, maintenance of phenotype and ectopic grafting, are also pertinent. The safety assessment would therefore consider both GT and SCT risks.

Conclusion

The range of potential therapies represented by ATMPs is vast and it is unreasonable to expect regulators to produce detailed guidance on all such developments. The risk-based approach recommended in the EMA guideline on cell-based medicinal products[15] and described in a draft guideline[17] is to be recommended because it puts the sponsor/developer at the centre of the process for designing the development plan. The risk-based approach is an iterative one that investigates the need for particular studies depending on the outcome of earlier investigations. It does not provide a definitive starting point for determining at what stage it is appropriate to progress to human subjects, but it does provide a structured way of identifying and assessing each individual risk, which is of benefit when departing from the conventional expectations of drug development. It is for the ATMP developer to critically assess the point at which an FIH study could be initiated, but as for many elements of the development process for these products, timely engagement with regulators and observation of scientific advice is critical.

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