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A regulatory perspective of clinical trial applications for biological products with particular emphasis on Advanced Therapy Medicinal Products (ATMPs)

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The safety of trial subjects is the tenet that guides the regulatory assessment of a Clinical Trial Authorization application and applies equally to trials involving small molecules and those with biological/biotechnological products, including Advanced Therapy Medicinal Products. The objective of a regulator is to ensure that the potential risk faced by a trial subject is outweighed by the potential benefit to them from taking part in the trial. The focus of the application review is to assess whether risks have been identified and appropriate steps taken to alleviate these as much as possible. Other factors are also taken into account during a review, such as regulatory requirements, and emerging non-clinical and clinical data from other trials on the same or similar products. This paper examines the regulatory review process of a Clinical Trial Authorization application from the perspectives of Quality, Non-Clinical and Clinical Regulatory Assessors at the Medicines and Healthcare products Regulatory Agency. It should be noted that each perspective has highlighted specific issues from their individual competence and that these can be different between the disciplines.

Introduction

The safety of trial subjects is the core principle under which the assessment of Clinical Trial Authorization (CTA) applications is conducted by the Medicines and Healthcare products Regulatory Agency (MHRA). This is particularly relevant to phase I, where there is no treatment benefit to subjects, but applies throughout clinical development and into phase IV (i.e. post-marketing) trials. It is this tenet that guides the regulatory assessment and applies equally to trials involving small molecules and biological/biotechnological products, including Advanced Therapy Medicinal Products (ATMPs). For each trial, subject safety must be balanced against the potential benefits available, so while the assessment principles remain unchanged, the level of risk considered acceptable for a potentially life-saving therapy will be considerably higher than that for a therapy with less radical consequences.

ATMPs are medicines for human use that are based on gene therapy, somatic cell therapy or tissue engineering [1]. They offer groundbreaking new opportunities for the treatment of disease and injury.

The objective to ensure subject safety is common between sponsor and regulator and the focus is on the ease with which risks to subject safety can be identified and alleviated. Naturally, other factors are taken into account, such as regulatory requirements, and emerging non-clinical and clinical data. In addition, control over

quality processes is expected to tighten as development proceeds and experience with the product increases.

We would recommend early dialogue between Investigators and the Agency, especially during the development of ATMPs, to avoid unnecessary work and potential delays.

Quality aspects

The ever-expanding array of biological/biotechnological products, including ATMPs, as compared with small molecules, together with the greater complexity of the manufacturing processes and the products themselves makes regulation of these products more challenging. By the very nature of experimental medicine, many products in early phase clinical trials are at the cutting edge of research with only a handful of individuals having expert knowledge of their characteristics and biological activities. The challenge for regulators is to identify potential risks and to ensure that sponsors put in place sufficient controls to reduce these to an acceptable level, commensurate with the potential benefit available from the therapy.

The risks from what might be described as conventional biotechnological drug substances, for example recombinant proteins, are well known and recognized strategies can be applied during the manufacture of these products to control risk. To use a straightforward example, adventitious contamination of a cell bank may be controlled through a combination of appropriate processing conditions and testing for viruses, bacteria, mycoplasma and endotoxin. Contamination during cell culture is again controlled via in-process testing of the cell culture harvest and at points throughout downstream processing as well during release testing of the substance. The risks presented by process-related impurities, for example host cell protein, host cell DNA, cell culture components and reagents used during downstream processing, are well characterized and recognized safe limits have been identified and can be applied. It is when the products, the manufacturing process and the raw materials or starting materials become more complex and less routine that the identification and mitigation of risk becomes more difficult.

The risks associated with ATMPs are more diverse in character because of the broader range of products covered by this title: gene therapy and somatic cell therapy medicinal products and tissue engineered products. The following (non-exhaustive) list of criteria may be used to evaluate the potential risk posed by the administration of cell-based medicinal products and to determine whether the controls in place are adequate: the origin of the product (autologous *vs.* allogeneic), the ability of the cells to proliferate and differentiate, the ability of the cells to initiate an immune response, the manufacturing process (e.g. the degree to which cells have been manipulated) and the presence of non-cellular components (e.g. inert scaffolds or bioactive molecules). Added to these are the usual considerations of the duration of exposure, which in the instance of cell products may correspond to the life span of the cell but for gene therapy products may be the life span of the trial subject, and the mode of administration.

It is impossible to provide examples for each criterion within the boundaries of this article but the following illustrates some of the potential challenges faced by regulators. Perhaps the first risk to be assessed is that presented from the cell origin. For example, pooling of cells from multiple donors adds to the potential risk in terms of undesired immunological responses in the recipient, variability in therapeutic activity and an increased risk of disease transmission. In these cases, the need for consistency in potency/activity has to be balanced against the inherent variability in biological products and need for realistic specification limits, particularly for early phase trials. Where primary cell isolates are used directly for cell-based products (i.e. without the establishment of a cell bank), there is often limited product available for testing. In these instances, the quality of the product is reliant upon control of the manufacturing process, for which limited data may be available upon which to make an assessment. Characterization presents a significant challenge, as the regulator may have little or no practical experience of the cells involved. Characteristics, such as cell surface markers, that are obvious to the researcher may be less apparent to the regulator and, therefore, it is important that the Investigational Medicinal Product Dossier (IMPD) not only provides confirmatory evidence as to the identity and activity of the desired cells but also discusses the potential presence of contaminating cells and, in the case of stem cells, control over differentiation of the cells.

As mentioned earlier, ATMPs encompass a wide range of product types with various characteristics that inevitably impact on their manufacture and control. This variability may also impact on some of the regulatory expectations for these products. For example, a cell therapy product comprising viable cells may need to be infused into the trial subject within hours of manufacture completion so as to ensure maximum efficacy. Under these circumstances, it may be permissible to infuse the cells before all release testing has been completed. Any such proposal would have to be fully justified and a clinical action plan in place in the event of unexpected or out of specification results arising post-infusion. A similar approach would not usually be justifiable for a traditional biological/biotechnological product or even other types of ATMP, such as viral vectors used for gene therapy, where frozen storage does not impact significantly on efficacy.

In summary, the challenge facing regulators from a Quality perspective lies in the identification of potential risk, particularly in the case of ATMPs. For researchers, the challenge lies not only in identifying the risk but ensur-

ing that the risk is appropriately controlled and that this information is communicated effectively to the competent authority in the CTA submission.

Non-clinical aspects

There are some differences in developing biological products compared with chemicals [2] and as mentioned previously, the risks associated with ATMPs are more diverse in character and creating a suitable non-clinical testing programme is extremely challenging. The development aim for all product types is, however, the same and can be stated as: (i) to provide evidence for belief in potential therapeutic activity and (ii) to provide data to enable safe clinical trials and characterize risks that cannot be assessed by clinical testing.

Evidence supporting (i) establishes the basic rationale for why the product could have therapeutic activity. This addresses its primary pharmacodynamic action. Questions addressed are:

- what is the biological target of the drug?
- how does it acts – agonist, antagonist or other?
- what are the biological consequences of this action?
- how does this relate to the disease and potential for benefit?

For each of biological and non-biological products, a set of data comprising quantitative estimates and qualitative descriptions of the effect of the test agent is needed and should be linked to the reason for expecting therapeutic benefit. For most products, this will relate to characterization of action at the primary pharmacodynamic target. Where the product comprises cells, the primary pharmacodynamic target may be unclear, but there must still be a justification for the proposed doses, e.g. in terms of cells per kg.

In some instances, for instance, gene therapy or cell-based products, the first human use of the product will be in patients, because such products cannot ethically be tested in healthy volunteers, as they may persist in the dosed subject for a very long time. In such cases, the dose selected needs to be justified with reference to the expectation for benefit. This resembles the development of anti-cancer agents in patients with advanced cancer where initial doses for humans are selected in order to offer potential benefit. For cellular products, doses should be related to those used in non-clinical studies. It can also be useful to relate proposed doses to those used in previous clinical studies with similar cell types, where such data are available.

Due to higher specificity of at least some biological products, testing for secondary pharmacodynamic effects tends to be more limited for such products. Receptor screening to identify off-target binding is not done and effects on vital functions (central nervous, cardiovascular and respiratory systems) can be screened in general toxicity studies.

For a viable product, pharmacodynamic actions must be expressed appropriately. A local anaesthetic used in dental extraction should have a short action, but an agent used in controlling pain after the procedure should act for several hours. By contrast, gene therapy to correct a genetic abnormality could persist for the patient's lifetime. As proteins are expected to be broken down to constituent amino acids, metabolism and excretion studies are not needed for ATMPs that contain proteins as the active agent.

Toxicity testing is conducted to address (ii) above, that is, to contribute to safe development of medicinal products in subsequent testing [3]. General toxicity testing should be done in species showing the primary pharmacological response and if there is a neutralizing immune response, as can arise with biological products, it may be that further testing is not warranted. Regulatory Agencies generally suggest a flexible, case-by-case, science-based approach to the non-clinical safety evaluation needed to support clinical development of biological products, which is even more necessary for ATMPs.

Studies still aim to identify the type of toxicity, its reversibility and to at what exposures it occurs. Characterizing exposure relies on toxicokinetic data [4].

Because many biological products are active only in non-human primates (NHP), reproductive toxicity testing poses particular challenges [5] and a case-by-case approach should be applied. Where an agent is only active in NHP, it is preferred to test in this species. An alternative is to develop a murine version of the product such that testing can be done in mice. Use of homologues is not preferred as it is rarely the case that the homolgous molecule has the same profile (e.g. affinity) as the product under development. However, if the product is not active even in NHP, then testing of a homologue may be the most appropriate approach.

Genotoxicity studies test effects on the genome. The nature of biological products means that they typically do not interact with the genome, making this type of testing irrelevant [6]. Despite criticism [7], carcinogenicity testing relies on lifetime studies in rodents. If the product is not active in rodents, as is often the case for biological products, such study designs are inappropriate [5, 8]. Where the product is active in rodents, and its use meets requirements for carcinogenicity testing, then this type of study is requested.

For cellular and gene therapy products, although the aims remain the same, to establish evidence supporting therapeutic potential and to support expectation of safe onward development, how this is achieved is somewhat different, because of the different nature of these products [9]. One difference from chemical drugs is that administered cells may persist for a prolonged period and testing

to determine safety of long term exposure is needed. This extensive exposure is fundamentally different from the life time exposure necessary for small chemicals used to treat chronic diseases such as diabetes and hypertension. Testing to determine safety of long term exposure should be prior to any human use [10] and, therefore, poses a high hurdle because this means that lifetime studies in rodents may be needed prior to any human use. Such testing also applies to stem-cell based products too [11, 12]. For cell-based products, their biodistribution and persistence is key in understanding their risk profile.

Many major currently marketed biological medicines, including some ATMPs, are, or soon will be, coming to the end of their patent protection. An increasing number of so called 'biosimilar' products are, therefore, under development, especially biosimilar monoclonal antibodies. For putative biosimilar products, the aim of development is to show that the new product is the same as the originator such that a truncated development can be justified. There is debate about the value of comparative *in vivo* testing [13, 14]. It could be argued that the objective of testing was achieved by development of the originator. Requiring comparative studies could result in the anomalous situation that much bigger toxicity studies are needed to eliminate possibility of difference than were conducted to establish safety of the originator product. At present, methods applied to compare structures of two biological products may not be sufficient to characterize the clinical significance of likely differences in large molecules, such as monoclonal antibodies, but, in conjunction with *in vitro* testing, they may suffice to show similarity of smaller biological molecules, so justifying an absence of comparative toxicity studies. Comparative *in vitro* studies to assess differences in binding or functions should be conducted first. In a second step, it should be determined whether additional *in vivo* non-clinical work is warranted. If an *in vivo* study is deemed necessary, the focus of the study depends on the need for additional information, and the availability of a relevant animal model. Regulations on Biosimilars within the EU are currently under review [15–17]. In the US, while a draft guidance on Biosimilars was released in 2012 [18], opinions on what the final regulatory standard should be are still very much undecided [19].

The nature of biological products means that some study designs standardized for use with chemical drugs [20] are not applicable. Table 1 presents a comparison. However, although study specifics may differ, the overarching principle is the same – to show reasons for expecting therapeutic benefit and to support safe continued development.

Clinical aspects

As with all investigational medicinal products (IMP), the primary focus of the clinical review of a CTA involving a biological product is safety. However, this is often analyzed against the putative benefits to the trial participants. The latter applies particularly later on in development when efficacy is more of a focus for a trial, but can be applicable as early as a first in man trial, for example for a gene therapy product that may have permanent effects after a single dose. Therefore, the protocol should contain an evaluation of the anticipated benefits and risks as required under the relevant Articles of Directive 2001/20/EC [21, 22]. A first time in man trial should also ensure all appropriate guidance has been followed including the EU guidance on mitigating risk in first time in man trials for medicinal products [23].

Risk identification and risk mitigation

The protocol should identify the risks associated with the biological based on previous experience with the same product and/or the same class of products, the mode of action, the nature of the target and the relevance of animal models (discussed above). Key aspects of the protocol should be designed to mitigate the identified risk factors, including:

- Study population/eligibility criteria: A rationale for the selection of subjects and appropriate exclusion of subjects who may be predisposed to developing adverse reactions from the biological (if such risks cannot be weighted against the perceived benefits)
- Dose: The dose requires detailed justification, particularly when this is expressed as a number of cells. Justification in terms of efficacy is also relevant for ATMPs where permanent effects may occur and first doses in humans would be expected to be safe but also be efficacious.
- Safety monitoring: The common adverse reactions to biologicals such as immunogenicity, infusion reactions, cytokine release, immunosuppression, etc. should be monitored via appropriate measures (clinical examination, observation of vital signs, laboratory tests, etc.). Although off-target reactions to biologicals are rare compared with small molecules, there are well-documented examples and any such effects should be adequately addressed in the protocol.
- Safety follow-up: Monoclonal antibodies have long half-lives whereas certain ATMPs may persist in the body throughout subject's life-span and consequently may give rise to delayed adverse reactions. Therefore, duration of follow-up should be adequate to monitor the development of such reactions. Serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports.

Immunogenicity

A key feature of the biologicals compared with small molecules is their ability to induce an immune response

Table 1

Comparison of study types required for 'small molecule' or biological products

	Small chemical product	Biological product
Primary pharmacodynamics	*In vitro/in vivo* studies establishing reason for belief in therapeutic potential	*In vitro/in vivo* studies establishing reason for belief in therapeutic potential
Secondary pharmacodynamics	*In vitro* screens to identify potential off-target binding with follow-up studies assessing functional effects	Typically, no studies done. Studies may be done to determine Fc-effects of an antibody acting by blocking a cell-bound target
Safety pharmacology	*In vitro* screens of interactions with proteins (e.g. ion channels) and of cellular effects; *in vivo* studies with focus on endpoints relevant to behaviour, heart electrical activity and blood pressure and lung function tests	No *in vitro* studies as there is little expectation of an effect on ion channels; *in vivo* testing is often included in general toxicity tests and only supplemented with dedicated studies if there is a concern
Absorption	Studies done to describe basic pharmacokinetic profile of bioavailability, elimination half-life and C_{max}/t_{max}	Studies done to describe basic pharmacokinetic profile of bioavailability, elimination half-life and C_{max}/t_{max}
Distribution	Describes the exposure of different organs over time, including regions of particular interest for therapeutic activity (e.g. brain) and for elimination routes (liver, kidney)	Not done, except for cellular and gene therapy products; to prevent vertical transmission, biodistribution to the gonads is of special interest for gene therapy products.
Metabolism	Describes the breakdown route – role of CYP P450s or other enzymes	Not done; breakdown is to smaller constituents such as amino acids
Excretion	Characterizes roles for e.g. renal, hepatic and biliary routes of elimination	Not done, except for virus-based products.
General toxicity	Two species dosed for up to 6 to 9 months	Typically, two species for short term testing and one species for 6 months*; single species where a second species is not pharmacodynamically responsive.
Toxicokinetics	Needed to support exposure in toxicity studies	Needed to support exposure in toxicity studies
Local tolerance	Usually included in general toxicity studies using clinical route of administration	Usually included in general toxicity studies using clinical route of administration
Genotoxicity	*In vitro* and *in vivo* effects to determine effects on the genome	Not done, as the product is not expected to interact with the genome.†
Carcinogenicity	Lifetime study in rats and/or mice using maximal tolerated doses evaluating incidence of tumours	Such studies are not done as most biological products do not have their primary pharmacodynamic action in rats or mice. Risk judgement is based on biological plausibility and *in vitro* data.‡
Reproductive toxicity	Fertility testing in males and females in one species; developmental testing in pregnant females in two species during organogenesis; developmental testing of offspring in one species	Dedicated fertility studies are rarely done. Developmental toxicity testing may comprise a single study in primates with dosing from early pregnancy until post-weaning.
Environmental risk	Assess risk of impact on the environment and describe actions needed to limit this if potential harm is identified	Not done (except for release of genetically modified organisms), given the nature of the expected breakdown of the product

*While ICH S6(R1) [6] states that for chronic use biological products, repeat dose toxicity studies of 6 months duration in rodents or non-rodents are considered sufficient and recognizes that studies of longer duration have not generally provided useful information that changed the clinical course of development, it is not clear whether global regulatory acceptance of a maximum of 6 months testing for ATMPs will be adopted. †An exception is integration testing where viruses are used to delivery gene therapy. ‡An exception is where the product may have long term persistence, e.g. cell based product or gene therapy.

through various mechanisms including the production of anti-drug antibodies. This may have clinical consequences such as generalized immune effects (infusion reactions, anaphylaxis/allergy, cytokine release and serum sickness), loss of efficacy, neutralization of the endogenous protein, or, very occasionally, enhancement of activity. Immunogenicity may also be related to the route of administration, dose and treatment duration, host's immune status (e.g. immunosuppressed patients may have decreased likelihood of antibody formation) and congenital deficiency of an endogenous protein (e.g. factor VIII, which increases the likelihood of an immune response to an exogenous replacement protein).

Group considerations

The safety considerations in a specific trial will depend on the nature of the biological product being administered, the study population (e.g. children, immunosuppressed patients, healthy volunteers, etc.) and the factors associated with the disease being treated. Whilst it is acknowledged that some areas, such as biosimilars, are not without their issues, there are specific issues related to certain groups of biologicals that warrant particular attention:

a) ATMPs

Sponsors should be aware of the specific regulations and guidance that apply to ATMPs [1, 24].

- Cell based Medicinal Products (Somatic Cell Therapy Medicinal Products and Tissue Engineered Products)
  - Basic constituents of these ATMPs are cells (either stem cells or differentiated cells) and considerations should be given to the following 'intrinsic' characteristics of the cells: origin (autologous *vs.* allogeneic), differential potency (pluripotent, multipotent,

unipotent or fully differentiated), proliferative capacity, life span, tumourigenicity, immunogenicity and biodistribution.
- ○ There are external factors that may influence the safety profile of these products such as the level of cell manipulation (number of clonal expansions, etc.) and the mode of administration.
- ○ Potential for the development of long term/delayed adverse reactions such as tumourigenesis (especially teratomas), development of autoimmune diseases, consequences of ectopic engraftment and unwanted differentiation should be considered.
- ○ The administration of these products often requires specialized procedures including surgery as well as administration of immunosuppressants – risks relating to these should be discussed in the protocol [8, 25].

• Gene Therapy Medicinal Products (GTMP)
- ○ Specific EU guidelines relevant to GTMPs are available [26, 27].
- ○ A GTMP typically functions as a sequence of different components – the vector and the inserted sequence(s), the target cells modified by the vector and the protein expressed upon successful gene transfer. Each of these components can contribute to the development of adverse events.
- ○ The vector's characteristics such as its type (plasmids *vs.* viral), persistence in the host, potential integration into the host's genome (e.g. gamma retro viruses and lenti viruses carry a high risk), potential for latency and reactivation, replication competence and biodistribution should be contemplated.
- ○ Additionally, persistence of the transgene, its antigenicity, its potential for integration and the duration of expression should also be addressed.
- ○ As with other ATMPs, these products also carry the potential to give rise to delayed adverse reactions such as germline mutation, tumourigenicity (through insertional mutagenesis and other mechanisms), generation of autoimmunity and reactivation of the vector with virulence. Consideration should be given for monitoring of these adverse reactions along with an adequate period of follow-up in line with existing guidelines [28, 29].

b) Vaccines
- • Administration of investigational vaccines to a healthy population especially when there are marketed alternatives warrants adequate justification of the subject selection.
- • When 'combined' vaccines are used, considerations should be given to immunological interference due to antigenic competition, epitope specific suppression, effect of the adjuvant and adverse adjuvant interaction.
- • The vaccine and any adjuvants are considered separately and any safety monitoring should also consider them separately.

c) Monoclonal antibodies
- • Monoclonal antibodies are highly immunogenic. The protocol should discuss the possible immune-related adverse reactions along with appropriate mitigation strategies, such as premedication prior to infusion, monitoring of vital signs during infusion and laboratory testing for the detection of anti-drug antibodies.
- • Humanized/fully human antibodies are generally less immunogenic compared with murine antibodies. However, any reduction in safety monitoring will still require justification. The prolonged half-life of antibodies will particularly have an impact on the duration of follow-up.

Conclusion

Biological products, and especially ATMPs, pose particular problems for the Regulatory review of a clinical trial application. The objective of a Regulator is to ensure subject safety and the focus of a review is on how risks to subject safety can be identified and alleviated, thus aiming to maintain an appropriate risk–benefit profile.

By the very nature of experimental medicine, many ATMPs in early phase clinical trials are at the cutting edge of research with only a handful of individuals having expert knowledge of their characteristics and biological activities. Early dialogue between Investigators and Regulators is encouraged to avoid unnecessary work and delays [30].

The risks from what might be described as 'conventional biotechnological drug substances' are, however, now reasonably well known and recognized strategies can be applied for these products to mitigate risk [22].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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