Clinical trial applications for biologicals – a UK regulatory clinical perspective

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Abstract
With increasing numbers of clinical trials involving biological medicinal products, they have become a topic of much discussion regarding quality, including the upcoming quality guideline, as recently discussed in this journal.1 But what of the clinical aspects to these trials? This article provides some insight into the review process of biological clinical trial applications (CTAs) by the MHRA Clinical Trials Unit (CTU) that may then assist in future applications. It should be remembered that, as with all clinical trials, academic and non-commercial trials are subject to the same scrutiny as commercially-sponsored biological trials regardless of the use biological products.

What are biologicals?
A biological medicinal product is a product of which the active substance is a biological substance. A biological substance is a substance produced by or extracted from a biological source and for which a combination of physico-chemical-biological testing and the production process and its control is needed for its characterisation and the determination of its quality. This definition is given both in Part I of Annex I of Directive 2001/83/EC (as amended by Directive 2003/63/EC) and in the introductory statements to Annex I of EC/1084/2003 and EC/1085/2003. According to this definition the substance should be of biological origin and, due to its complexity, a combination of physico-chemical-biological testing together with testing and control of the production process is needed for its characterisation and determination of quality.

Under this definition therefore are included recombinant proteins, monoclonal antibodies, immunological medicinal products such as sera and vaccines, allergens, and advanced therapy medicinal products (ATMPs). ATMPs include gene therapy products, somatic cells and tissue engineered products that also meet the definition of a medicinal product. There are other products not able to easily be assigned to one of these categories but nonetheless are regarded as biological medicinal products in current legislation. These include substances such as heparin, bovine and porcine insulin and many others. A non-exhaustive list of these is available on the Heads of Medicines Agency website.2

In the case of advanced therapy products, there is sometimes the need for judgement as to whether a product falls outside the definition of a medicinal product and thus outside the remit of the clinical trials regulations. Advice can be sought from the MHRA in this regard if there is any doubt.3

Why are biologicals different?
The regulatory approach to biologicals differs to that of non-biologicals in that there is generally an added degree of complexity and thus some routes to marketing authorisation, such as bibliographic applications, are not normally applicable. This may then impact on the development programme and design of clinical trials required to support a future marketing authorisation application (MAA). The production of biologicals may also involve living sources and is generally more complex than for small molecules, with a greater possibility of changes in characterisation, and major implications for the end product and safety profile.

Biologicals development also includes the production of biosimilars. The nature of the differences in biologicals to other products, particularly in terms of quality, means studies of biosimilars may have significant differences to studies for other generic products. A more stepwise approach to development is required and there is far greater emphasis on safety than for non-biological generic studies.

Biologicals are also more likely than small molecules to be immunogenic. This may not always be clinically relevant but it can lead to serious reactions and autoimmune reactions. Neutralising antibodies can also have a major effect, primarily on efficacy, but any safety implications must also be considered. The clinical outcome can vary but includes cytokine release, hypersensitivity, immunodeficiency and cross-reactivity.4

General considerations for a CTA
The same legal obligations in place for clinical trials of non-biologicals also apply to biologicals. Under these regulations a trial cannot be initiated unless approval has been granted from the appropriate national competent authorities and a positive opinion from ethics committees and other local committees received.

The main legal obligations are set out in the following documents:
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice with regard to investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- The Medicines for Human Use (Clinical Trials) Regulations 2004 – SI 2004/1013, plus all subsequent amendments. This is specific to the UK. The specific requirement for written authorisation before starting a clinical trial with a biological is covered in the Clinical Trial Directive Article 9(5).

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Overall, sponsors will be expected to have considered the likelihood and magnitude of any potential harm to individual patients participating in the trial. This potential for harm should be considered against the potential benefits to individual participating patients, as well to patients who will suffer from the condition in the future. The discussion is expected to be included in the protocol, together with details of all safety monitoring and risk mitigation, since the protocol is considered the definitive document and the document against which action is executed.

The same rules and principles for the statistical plan apply as for any other trial. It is acknowledged that biologicals may provide novel hurdles to power calculations but the sample size should be justified on the basis of the study objectives and in terms of performance characteristics of the trial. Small trials are not discouraged, but any lack of precision should be clear and any limitations should be evident.

As with non-biological CTAs, the MHRA is open to consideration of adaptive designs for biological trials, as long as adequate justification and monitoring is provided.

Specific considerations for a biological CTA

The focus of the clinical regulatory review of a CTA for a biological product, as with all products, is safety. There has been significant action post-approval for biologicals, often in the form of a Direct Healthcare Professional Communication (DHPC), and this highlights the need for additional vigilance pre-approval that warrants stringent safety monitoring earlier in development.1

Preclinical considerations: This article will not specifically address preclinical issues and concerns, but it is important that the protocol includes a discussion of the relevance of preclinical data, in particular when this is deemed to be less relevant due to, for example, lack of appropriate animal models. Pharmacological action, immune effects and pharmacokinetic (PK) properties all require careful consideration and discussion.

Risk minimisation considerations: The protocol should specifically address each potential risk in terms of how it has been mitigated in the study. This will include mitigation steps through carefully specified eligibility criteria and specific safety monitoring during treatment. Specific actions and management will also be required for certain risks such as infusion reactions, infection risks and other more specific events as appropriate to that product, for example reversible posterior leukoencephalopathy syndrome (RPLS). Safety follow-up, and contraceptive precautions after treatment has ended, are also areas required to be specifically addressed. There should be continued safety monitoring (which can be less intense than during treatment if justified) and justification for the length of time for which follow-up will continue. For example, some biologicals have half-lives much longer than the average for chemical entities, or have a persistent effect as in the case of rituximab, which should be taken into account in establishing the duration of safety follow-up and contraceptive requirements.

It may also be appropriate within the protocol to include a discussion of other similar products with a similar mechanism of action and their adverse event profile. This will help direct investigators to other potential risks and how these have been addressed in the trial.

A general discussion of the overall benefit-risk for the proposed indication is required, considering that this can differ significantly, for example between an investigational medicinal product (IMP) for a rare disease with limited treatment options and one to be used as a prophylactic vaccine in an otherwise healthy population.

A first-time-in-man (FTIM) trial should also ensure all appropriate guidance has been followed. This includes the EMA guidance on mitigating risk in FTIM trials for medicinal products.2

Group considerations: The safety considerations in a trial will clearly depend on the specific nature of the product being administered. However there may also be more general areas that require thought and possible discussion and actions based on more general group characteristics, as in the examples below.

1 Vaccines
   - Consideration must be given to use of the product in a generally healthy population. This should include careful eligibility criteria
   - The vaccine and any adjuvants are considered separately and any safety monitoring should also consider them separately.

2 Monoclonal antibodies
   - Monoclonal antibodies by their very nature are immunogenic and this must be fully discussed in the protocol. Management of potential reactions must also be included.
   - Chimeric and humanised antibodies generally have reduced immunogenicity, compared with murine antibodies, but have an increased half life, all of which requires consideration in the protocol. Half life will particularly have an impact on the length of follow-up and justification for how long follow-up continues is expected.
   - Fully human antibodies may be the least immunogenic but any reduction in safety monitoring will still require justification.

3 Advanced therapies
   - This covers a significant area and would generally warrant several articles on its own as a topic, but a brief outline is included here.
   - Sponsors should be aware of all the specific regulations and guidance that apply to ATMPs:
     - Detailed guidelines on good clinical practice specific to advanced therapy medicinal products.


Gene therapy:
   - Delivery mechanisms also require assessment and consideration in a CTA. The vector should be discussed in terms of organ tropism, biodistribution, chromosome integration, latency and possible reactivation, persistence of expression, replication competence, altered expression of host genes, unintended biodistribution
   - Specific EMA guidance is available and sponsors should be familiar with all documents relevant to their product.

The protocol should include a discussion that gives consideration to the source of any cells, either autologous or allogeneic.

   - Autologous:
     - These would be expected to be less immunogenic than allogeneic cells but this must still be justified and appropriate safety measures included in the monitoring plan.

   - Allogeneic:
     - Note should be made of the potential to invoke considerable immune responses in a patient
     - Tissue typing is possible and may be expected, eg, human leukocyte antigens (HLA) typing. It is worth noting that other antigens can induce immune responses too, such as mitochondrial proteins, and would be expected to be discussed as appropriate

   - A sponsor should consider whether patients need...
Tissue engineered products are also specifically covered by the ATMP regulations. Engineered is given as including cells or tissues that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties have been achieved, or the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor. If there is any doubt as to whether any manipulation is considered as engineering this should be discussed with the MHRA.

- Specific consideration is required to the patient population in terms of benefit–risk. This includes justification in terms of quality of life, co-morbidity and age. In particular those who are younger may be considered to have greater benefit, but this should be weighed against the longer lifespan and possible increased risk of developing longer term adverse effects.

**Evolving challenges for assessment of biological clinical trials**

The science of biological compounds continues to progress and produce innovative products with new mechanisms of action. The benefit–risk should be considered at every stage of development and safety of trial subjects is key. Potential risks will be based on preclinical data, but the challenge is to predict those that may not be so readily foreseen. With products targeting ever more specific immune cells and receptors, predicting the safety profile is becoming the main challenge. Any CTA should address this in detail and have in place all relevant measures to reduce the risks, including monitoring for possible risks.

A future challenge, and one that has not been so prominent in recent years but may well become more of a focus in future, is the challenge of trials with biological products in children. The paediatric regulations have been in force for some years and while there have been numerous paediatric investigation plans (PIPs) approved, many products have either waivers or deferrals in place. Experience in conducting paediatric trials of biologicals is therefore still limited, both by companies and regulatory agencies.

There are often unknowns when preparing a CTA and sponsors should be aware that face-to-face scientific advice is always available to discuss issues and to provide clarification. This is particularly pertinent for biological products where written guidance may not be able to provide answer or is simply not available.

### Useful contact information

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### References


3. Information available on the MHRA website at http://www.mhra.gov.uk/hwwereregulate/Advancedtherapeuticalmedicinalproducts/FAQs/index.htm3

