Focus – Biotechnology

Considerations in the clinical development of biotech medicines

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Abstract
Development of biotech medicinal products presents a number of challenges. These can arise from the therapeutic area under investigation – many product applications are in therapeutic settings such as oncology or rheumatology, where ethical considerations must be observed. However, by the very nature of protein therapy, immune responses can lead to a lack of efficacy or adverse events in the patient. Immunogenicity can be triggered not only through the nature of the product but also external influences on the protein structure. Manufacturing development and scale-up to meet demands of large-scale clinical trials should be considered in parallel with clinical scrutiny – comparability is critical in this process. Therefore the design of the clinical programme must take into account many factors, but also generate compelling data to establishing therapeutic efficacy.

Background
Biological medicinal products now play a critical part in the fight against disease. The first biologicals were vaccines and anti-toxins which, in Europe, have their origins from the work of Edward Jenner in the late 1700s. Insulin, discovered in 1921, is the earliest example of a replacement protein; this was later followed by blood products and other human hormones such as somatropin and follicle-stimulating hormone (FSH). However, the use of biologicals and human derived material in particular was associated with a high risk of inadvertent transmission of human pathogens resulting in incidences of Creutzfeldt–Jakob disease (CJD) associated with human derived growth hormone,1–4 HIV,5–8 and hepatitis,9,10 associated with Factor VIII.

Clearance of prions remains a challenge.

Once the risk of iatrogenic transmission of viruses was appreciated, methods were established for the removal of enveloped viruses through solvent detergent treatment. However clearance of non-enveloped viruses remained challenging until relatively recently, with the introduction of nano-filtration and other innovative clearance procedures in the past ten years. Clearance of prions remains a challenge.

The contamination of human derived growth hormone with prions led to its complete withdrawal in the early 1980s until it could be replaced some six months later with rDNA-derived methionyl human growth hormone. The application of recombinant DNA (rDNA) technology in the 1980s offered not only safer and more reproducible production technology but also the ability to manufacture proteins that had been difficult to extract, such as epoetin and the interferons; designer proteins such as insulin analogues; and more significantly the monoclonal antibodies. The ability to tailor antibodies to target an array of receptors and pathogens has resulted in the development of some of the most successful drugs ever produced, particularly in the fields of rheumatology and oncology. These include blockbusters such as Herceptin, MabThera, Avastin and Erbitux in oncology, and Remicade, Humira, Enbrel and MabThera in rheumatology.

The development of biological medicines presents many challenges, even in the nonclinical setting. Difficulties encountered include species specificity, where the protein is pharmacologically active in few or no species other than man, and immunogenicity. Immune responses may neutralise the protein, nullifying its effect and so limiting the value of nonclinical studies. In these circumstances there will be the need to proceed cautiously into Phase I, starting with low doses in a few volunteers and introduction of sentinel groups. Furthermore for biologics, the use of an arbitrary safety factor may be too simplistic an approach because results in the animal model may not be clearly translatable into an expected clinical effect in human subjects. Thus, additional considerations such as the calculated percentage receptor occupancy and “minimal anticipated biological effect level” (MABEL), based on predicted plasma levels as a function of the in vitro biological effect, ought also to be considered in setting the target dose.

Pharmacodynamics has a key role to play

Biotech products may have a highly specific and easily measurable pharmacodynamic action, notably products such as insulin (lowering of blood glucose), epoetin (increasing haemoglobin level), blood factors and filgrastim (increasing neutrophil count). In these circumstances, and particularly where rDNA proteins are intended to replace naturally extracted proteins or in the development of biosimilars, pharmacodynamic data can play an important role in establishing therapeutic equivalence and so reduce the need for later phase studies. This has been the case in the development of recombinant human-insulin, human follicle-stimulating hormone12 and somatropin, where prior experience on the human derived protein existed. However confirmatory Phase III studies would still normally be required.

Phase I data will also help establish the most appropriate route of administration and optimal dosage. Human pharmacological studies thus play a critical role in establishing early safety and efficacy for a range of novel and biosimilar biotech products.

Phase II is often abridged, sometimes bypassed

The easily measurable pharmacodynamic effects of some biotech products can make their therapeutic potential relatively easy to determine using surrogate endpoints, ie, endpoints which can be correlated with a clinical effect without the need for long term studies to establish efficacy. Examples of surrogate endpoints include neutrophil count as opposed to febrile neutropenia, with filgrastim use in chemotherapy and follicle count as opposed to successful pregnancies with human follicle-stimulating
hormone. As already discussed, this enables much more information to be gleaned from Phase I studies than is often possible for small chemical entities. In these circumstances, the Phase II programme can be more targeted and sometimes completely bypassed.

Phase II studies, nevertheless, are important in helping to establish an optimal dose and the frequency of dosing. For biological products, fixing an optimal dose can be somewhat of a challenge. In some cases, notably insulin, dosage is dictated by individual needs and no recommendation can be made at all. But many biologicals, particularly many monoclonals, are relatively non-toxic, making it difficult to establish a maximum tolerated dose. A review of the development of most monoclonals will reveal very limited dose ranging work, particularly in oncology. One example is in the development of Herceptin,13 where dose ranging was conducted only at the pharmacokinetic level to establish the dose required to maintain an effective plasma level. In the case of MabThera, 500 mg and 100 mg doses were trialled in rheumatoid arthritis with very little difference in effect between the doses; the 1,000 mg dose was consequently selected.14 Generally, the optimum dose becomes the dose at which the therapeutic response levels off. However, this can be extremely difficult to ascertain, particularly where effects may only become evident over an extended time period, and one can speculate that quite often doses are set higher than is necessary.

Frequency of dosing is another important consideration. More frequent dosing might be expected to enhance efficacy but this could be at the expense of convenience and compliance, especially as protein-based medicines are almost invariably parenteral. It may be expected that dosage frequency ought to be based on plasma half-life, but many products which have a relatively short half-life can set off a chain of events that lasts for extended periods allowing weekly, monthly, bimonthly (eg, Remicade) or more frequent dosing. This can be extremely difficult to ascertain, particularly where effects may only become evident over an extended time period, and one can speculate that quite often doses are set higher than is necessary.

Another example is the development of coagulation factors and most protein-based medicines are relatively non-toxic, making it difficult to establish a maximum tolerated dose. A review of the development of most monoclonals will reveal very limited dose ranging work, particularly in oncology. One example is in the development of Herceptin,13 where dose ranging was conducted only at the pharmacokinetic level to establish the dose required to maintain an effective plasma level. In the case of MabThera, 500 mg and 100 mg doses were trialled in rheumatoid arthritis with very little difference in effect between the doses; the 1,000 mg dose was consequently selected.14 Generally, the optimum dose becomes the dose at which the therapeutic response levels off. However, this can be extremely difficult to ascertain, particularly where effects may only become evident over an extended time period, and one can speculate that quite often doses are set higher than is necessary.

Phase III presents new challenges
Phase III may require recruitment of hundreds and maybe thousands of patients, introducing further challenges. Patient numbers are driven by a number of factors. With respect to demonstration of efficacy these include: the choice comparator, ie, placebo-controlled trials require fewer patients than active comparators since the magnitude of effect will be greater when compared to placebo. In some cases the effect is so dramatic that comparison to historical data can suffice without the need for a comparator, as has been the cases in ultra-orphan diseases such as the development of Cerexyme for the treatment of Gaucher Disease, which included just 40 patients in the development programme.15 Another example is the development of coagulation factors and most notably the development of Factor VIII (NovoSeven) in the treatment of acquired haemophilia, which included 67 patients in the entire development programme.16

The difference in effect between the test product and comparator is a very important driver in determining the size of study required to achieve statistical significance. Safety considerations set against benefit-risk are also important in establishing the size of the trial programme. For example, vaccines administered widely to a healthy population need to demonstrate a high level of safety in tens of thousands of patients, whereas for a highly effective oncology product, safety becomes less critical compared with the consequences of lack of efficacy.

One of the greatest challenges in moving to Phase III is the need to increase production capacity to meet the greater need for clinical trial supplies to treat more patients over a longer time frame (typically six months to many years). Thus the limited availability of supplies may be a key constraint to expanding the Phase III programme.

Production scale-up often involves process optimisation and the resulting changes can introduce potentially undetectable alterations to the protein, which could impact safety and efficacy and so limit the value of existing studies. Consequently, before the Phase III supplies can be committed to extensive trials, comparability studies will be required and this may occasionally need to include bridging nonclinical, human pharmacodynamic and pharmacokinetic bioequivalence studies. Additionally during Phase III, changes might be introduced to the formulation or presentation of the product, for example in order to improve stability or introduce convenient delivery systems such as pen injectors, and this too will need to be supported by data. The impact of formulation change on safety was dramatically highlighted when the formulation of Eprex (epoetin) was changed to replace human serum albumin with polysorbate 80. This resulted in an increase in the incidence of neutralising antibodies, which also neutralised endogenous epoetin, giving rise to a debilitating condition known as Pure Red Cell Aplasia (PRCA).17 Although this condition affected only one in 10,000 patients, the only treatment at the time was regular blood transfusions. The cause of the problem was reported to be an interaction between the polysorbate and the rubber closure, generating leachate which seems to have acted as an adjuvant, so enhancing immunogenicity.18 Ironically, the change in formulation was introduced on the request of the CHMP so as to avoid use of human derived albumin in a recombinant-derived product. Another lesson from this incident is that it is impossible to fully establish safety in clinical development, even in programmes involving many thousands of patients, and post-marketing risk management programmes form an essential part of drug development to detect rare events.

Confirming efficacy
The regulators will require solid evidence for efficacy and usually this can only come from large Phase III studies. Efficacy is most convincingly demonstrated by demonstrating superiority over placebo or existing standard of care. Proving superiority over current treatment can be a tall order and so placebo-controlled studies are certainly the easier option. But placebo-controlled studies may not be ethical, particularly as biotech products are frequently used for the treatment of serious and life-threatening diseases, where to withhold treatment, cannot be justified. Some biotech products represent major therapeutic advances, enabling superiority over existing treatments to be demonstrated relatively easily. Sometimes the need to demonstrate superiority becomes absolute, for example where the new therapy is more toxic, or to justify the use of a more complex and expensive therapy over a current simpler and cheaper alternative. In other circumstances, such as Factor VIII as mentioned earlier, the therapeutic effect is so clear-cut that non-comparative studies are accepted by both CHMP and US FDA guidelines. Non-comparative studies may also be accepted in the development of orphan enzyme replacement therapies.

In other circumstances, rDNA-derived products have been developed as a replacement for a human or animal derived protein or as improved versions of existing products offering greater convenience or as biosimilars. In these circumstances demonstration of non-inferiority or equivalence is all that is required. However non-inferiority trials are associated with numerous challenges. First and foremost there is a need to present a case, based on historical data, that if placebo were to be...
included, an acceptable difference (delta) from placebo could be expected and that the preset non-inferiority or equivalence margin would not be so broad as to embrace the placebo effect. Generally there will be the need to show that there is a 95% certainty that at least 50% of the efficacy of the comparator would be preserved for the test product. To demonstrate non-inferiority or equivalence to these standards requires much larger studies than are needed to establish superiority over placebo.19,20

Biotech products are administered parenterally; this places further ethical constraints on the widespread use of placebo-controlled trials. Nevertheless, placebo injections have been accepted in many clinical trials. In some situations the need for infrequent doses reduces concern, so that monthly placebo injections in children under two years of age were accepted in trials of Synagis (palivizumab) for the prevention of respiratory syncytial infection in at risk children.21 However, views will vary between countries, ethics committees, companies and investigators, and each individual compound will need to be evaluated with respect to its own merits and the prevailing views at the time.

The ethical constraints on the use of placebo injections also prevent the use of double dummy designs constraining the ability to blind studies. Blinding is further confounded by the fact that biotech products often have highly specific and easily recognisable pharmacological effects. Blinding should be preserved as far as possible, for example by using different personnel for administration of the drug from those involved in patient assessment.

Safety data
Where a protein has not been available for therapeutic use prior to its biosynthesis, there will be no previous knowledge to base an evaluation of safety and efficacy. Thus, a more extensive clinical development programme is essential.

The most frequent problems associated with the therapeutic use of recombinant proteins arise from their immunogenicity. Proteins are by nature immunogenic, particularly if they are structurally altered. Antibodies generated against therapeutic proteins may be binding or neutralising. Neutralising antibodies bind to the active moiety of the protein, thereby reducing or even eliminating their therapeutic effect. Binding antibodies may interfere with bioavailability and plasma clearance. Furthermore, antibodies can precipitate a range of adverse events from mild injection site reactions to more wide-spread cutaneous reactions, to systemic effects such as arthralgia and fever and, rarely, to life-threatening anaphylactic type reactions. Antibodies against therapeutic proteins may also cross-react with the natural occurring proteins, as has been described earlier with respect to epoetin, and thereby potentially induce autoimmune disease. It is thus important to monitor antibody formation in all clinical trials conducted on biotech products and to monitor post-marketing for rare effects that might arise as a consequence of immunogenicity, particularly where the potential exists for anti-drug antibodies to cross-react with endogenous proteins.

Conclusion
The clinical development of biologics presents numerous challenges, ranging from running and interpreting nonclinical studies through to demonstrating efficacy in Phase III. Efficacy is most convincingly demonstrated in superiority studies but often placebo-controlled trials are not ethical or practical. In rare circumstances where efficacy is indisputable, non-comparative studies could be accepted. Often non-inferiority or, for biosimilars, equivalence trials are required and these are associated with several challenges. The most frequent problems associated with the therapeutic use of recombinant proteins arise from their immunogenicity and it is always important to monitor anti-drug antibody formation in all clinical trials conducted on biotech products.

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