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Review

Regulatory issues for phage-based clinical products

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Abstract: Phage-based therapeutic products are members of a growing and diverse group of products categorised as 'biologics', 'biologicals' or 'biotechnological products'. They are regulated in much the same way as conventional drugs although in America they have their own division at FDA, the Centre for Biologics Evaluation and Research, 'CBER' (as opposed to 'CDER', the corresponding drugs division). The distinction is important because there are significant differences between the two divisions in the amount of toxicological characterisation, clinical testing and manufacturing data that must be submitted for approval. Also, there are important differences in the extent to which multiparty manufacturing arrangements are permitted. There are a number of regulatory issues surrounding phage-based clinical products that, if addressed early during product development, will not become blocks to progress later on. The regulatory issues arise in part because of the unique nature of phage-based clinical products and in part because of their intended clinical use.

Keywords: bacteriophage; regulatory issues; phage-based clinical products

ISSUES ARISING FROM THE UNIQUE NATURE OF PHAGE-BASED CLINICAL PRODUCTS

Being based on bacteriophages, phage-based clinical products do not readily fall into the scope of existing regulatory guidelines. So, a major issue is deciding which particular guidelines apply to phage-based clinical products.

For example, there is a regulatory guideline[1] on specifications, test procedures and acceptance criteria for biotechnology products. The guideline applies to products from recombinant or non-recombinant cell culture expression systems that can be highly purified and characterised. Specifically included in the guideline are proteins and polypeptides, their derivatives and products of which they are components. Specifically excluded are antibiotics, synthetic peptides and polypeptides, DNA products and conventional vaccines. The question is, does this guideline apply to phage-based products? Are they included because they are 'proteins and polypeptides, their derivatives and products of which they are components' or excluded because they are 'DNA products'?

Similarly, there is a regulatory guideline[2] on preclinical safety evaluation which applies to products derived from characterised cells through the use of a variety of expression systems including bacteria, yeast, insect, plant and mammalian cells. Here, the guideline specifically includes, again, proteins and peptides, their derivatives and products of which they are components and those types of material derived from cell cultures or by using recombinant DNA technology. The guideline specifically excludes antibiotics, allergenic extracts, heparin, vitamins, cellular blood components, conventional bacterial or viral vaccines, DNA vaccines, cellular and gene therapies. Again, the question is are phage-based products included in this guideline? The same question can be asked in relation to a number of other guidelines that are available for biological products. Whether or not it is clear that phage-based products are covered by the guidelines, they should be read in order to understand the types of factors that regulators are interested in and to intelligently select those that clearly do relate to phage-based products. If that is done then a number of key issues that should be addressed during development will be identified. These issues are discussed in the following sections.

Cell banking

Quality concerns with cell-derived biological products arise from the potential presence of adventitious contaminants or from the properties of the cells used to prepare the product. From a regulatory perspective it is therefore important that appropriate quality controls of cell substrates and the events surrounding their preparation are in place. This means being able to provide documentary evidence about the source, history and generation of the cell substrate, and about

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the cell banking system and banking procedures that have been and will be used to ensure its continued supply.

Raw materials

The identity, purity and quality of raw materials are important as with all pharmaceutical products. A range of identity tests should be used to confirm that the banked cell is what it is purported to be. Purity tests, to show the absence of adventitious microbial agents and cellular contaminants, will include tests for mycoplasma, viruses and for contamination by other cell lines that may have been introduced inadvertently during cell banking procedures. Of particular and increasing concern with biologics is the possibility that raw materials derived from animals (especially from ruminants) may enable the spread of transmissible spongiform encephalopathies (TSE).[3] The term raw material includes materials and reagents such as bovine serum albumin, enzymes and culture media used in production and in the preparation of cell banks. It also includes materials such as media used in validation work that come into direct contact with manufacturing equipment. Thus it is essential either to avoid the use of such materials or to use materials derived from animals reared and killed in areas of the world that have no or few reported cases of indigenous TSE. A very recent requirement of the UK Medicines Control Agency (MCA) is that manufacturers of medicinal products must provide a signed declaration of compliance with European guidelines[3] on minimising the risk from transmissible spongiform encephalopathies via medicinal products.

Process controls

Process controls are more important with biological products than with conventional drugs. Biological products are generally complex mixtures of active and inactive components derived from, or consisting of, cell metabolites, cell debris, ingredients of culture media and the reagents used in extraction and purification processes. Such mixtures are difficult or impossible to characterise by analytical techniques. It follows that controlling the process is the key to ensuring the quality of the finished product. That can be done by performing appropriate tests at critical processing stages, comparing the results with specifications or action limits and making decisions about subsequent processing. The results of in-process testing can also be used to confirm the consistency of the process and may reduce or eliminate the need for finished product testing.

Viral contamination

If materials of animal (or human) origin are used in biotechnological production processes there is a risk that the final products will be contaminated with viruses. Contamination may come from raw materials used in the production process, for example peptone in growth media, from contaminants introduced within cell cultures and also from inadvertent contamination by operators. A combination of approaches is recommended[4] to control potential viral contamination of biologicals:

- selecting and testing source materials for absence of viruses
- testing the capacity of the production process to remove or inactivate viruses
- testing the product at various stages of production for absence of viruses

Bearing in mind the similarity of phages to human viruses it seems unlikely that phage production process would have significant capacity to inactivate or remove viruses. Regulatory authorities will therefore expect greater emphasis to be placed on testing source materials, and the product at various stages of production, to provide adequate levels of assurance that the final product is free of viral contamination.

Product characterisation

The importance of process controls in ensuring the quality of the finished product was explained above. However it is still necessary to characterise the finished product. Phages are complex structures and, as noted above, they exist in a complex mixture of cell metabolites, cell debris, ingredients of culture media and the reagents used in extraction and purification processes. The characterisation of such products to the extent required by regulatory authorities is a major challenge, even with, or perhaps because of, the variety and sophistication of characterisation methods that are available.

During development characterisation will be extensive and include determination of physicochemical and immunochemical properties, biological activity, purity and the nature of impurities.[1] In each case several complementary techniques may be used to maximise the extent and reliability of the information obtained. Regulatory authorities will expect to see realistic specifications that ensure adequate levels of purity, and safety for products used in clinical trials. Information obtained on those products will form the basis for setting and justifying acceptance criteria for the potency and efficacy, as well as the purity and safety, of the product that will be commercialised.

Issues arising from intended clinical use of phage-based products

Issues arising from the intended clinical use of phage-based products are the same as for other types of investigational medicinal product. However, understanding the issues and dealing with them are fundamental to successful product development. Even so, the issues are often overlooked, causing significant delays and additional costs to development programmes. Scientists involved in the field of phage therapy may not be familiar with the drug development process so It is appropriate to highlight some of

the critical topics that must be considered in the preparation of phage-based products for clinical use.

Stability

The stability of phage-based clinical products is important because they must have a shelf-life long enough to span the time needed for quality control, packaging and labelling, distribution to clinical study sites, storage during patient recruitment and for the duration of the study. For early phase clinical studies it may be possible to overcome a shortage of stability data by manufacturing the product in small batches at frequent intervals. A drawback to that approach is that batch to batch variations in the product, not detected by quality control testing, may affect the results of the clinical study. For later phases of clinical development it is unlikely that stability data justifying a shelf life of less than 6 months will be adequate. However many stability data are available it is generally prudent to generate stability data concurrently with the clinical study data on the batch of material that is actually used in the study.

Blinding

It is often necessary to conduct studies with some degree of blinding so that either the patient and/or the person administering the treatment is unaware as to whether the patient is receiving the active material, a placebo or a comparator product. The development of a placebo to match a phage-based clinical product may be a significant undertaking. A product that looks and, in some cases, tastes the same as the investigational product must be formulated, characterised, quality controlled and stability tested. It is even more difficult to formulate comparative products of established therapeutic agents that match the appearance of investigational products.

Clearly, the provision of placebos and comparators is a major consideration in the planning of clinical trials. Never the less, the time and resources needed to develop them are often underestimated or completely overlooked by those responsible for study planning.

Good manufacturing practice

Good Manufacturing Practice is the set of documented procedures and controls that manufacturers are legally required to apply to the manufacture and testing of pharmaceutical products. Although there is currently no legal requirement to manufacture clinical products according to the requirements of GMP there are very clear guidelines[6] that clinical products should be produced according to the principles of GMP. A common reaction to this, especially for early phase clinical studies, is that it is unduly onerous and will delay the start of clinical work. Yet the requirement makes good sense for two reasons. Firstly, the overriding purpose of GMP is to ensure that patients receive medicines that are of known potency and purity (and, in the case of marketed products, of known safety and efficacy). That can be no less important for patients (or volunteers) receiving investigational medicinal products. Secondly, the results of early phase clinical studies are often unexpected. In looking for an explanation for unexpected results attention usually turns first to the quality of the products used in the study. Allegations of mix-ups between active and placebo products are common. Without the documentary evidence that GMP provides there can be no conclusive proof that mix-ups or other errors have not been made. Thirdly, all aspects of the development of a new product are open to scrutiny by regulatory authorities. Shortcomings in the documentary evidence of the satisfactory conduct of any part of the development process could lead to approval being delayed whilst questions are answered or, perhaps, work is repeated.

Sterile Products

Products to be administered by parenteral routes must be sterile. GMP guidelines for investigational medicinal products require that they be sterilised by processes that are validated to at least the same degree as processes used to sterilise marketed products. This is an important factor with implications additional to those raised by the basic requirement for the application of GMP. The validation of sterile processes involves a large amount of work and may require the preparation of additional quantities of product. If the need for sterile processes to be validated is understood and accepted the necessary work and time can be factored into the development programme and their potential to lengthen development time can be minimised.

SUMMARY

So, in summary, it is important to interpret relevant guidelines for biological products to make intelligent decisions about which parts of the guidelines apply to phage-based products. Talk to regulatory authorities, they really are there to help especially at early stages of clinical studies with new types of therapies.

Next, look forward, think about the ultimate objective that you are trying to reach which is a commercialisable product and if that is the goal you wish to achieve, then the work that you do has to be done to appropriate standards that will withstand inspection by regulatory authorities. It is also useful to look backward from the point of view of a regulatory inspector. What will the regulator make in five/seven years time of the work that you are doing today? Will the records you are making today support a future product licence application.

And lastly, I'd encourage you to assume success. By assuming success, you are more likely to take the right approach in designing experiments and in the quality standards that you apply in conducting work to ensure that the work only has to be done once and will be acceptable to regulatory authorities.

A NOTE ABOUT THE INTERNATIONAL CONFERENCE ON HARMONISATION

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. This Mission is embodied in the Terms of Reference of ICH.

http://WWW.ifpma.org/ich1.html

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