DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(17), 2449-2463 (1990)

CHARACTERISATION OF MACROMOLECULES USED AS PHARMACEUTICAL EXCIPIENTS

EXCIPIENTS AND THE REGULATORY AUTHORITIES

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ABSTRACT

The sources of information on regulatory requirements for licensing (marketing authorisation) of pharmaceuticals in the European Community, including aspects applying to macromolecular excipients, are identified. The pharmaceutical, preclinical and clinical implications are discussed in outline.

PHARMACEUTICAL EXCIPIENTS

For the purpose of this paper 'pharmaceutical excipients' will be taken to include any material present in a formulated product which is not an active ingredient. It must be noted that in certain circumstances an 'excipient' can become an 'active ingredient'. [For example, poly(lactide-glycollide)

may be an excipient in an implantable drug delivery system but an 'active' in an absorbable suture, or sodium hyaluronic acid may be an 'active' or an excipient depending on the uses claimed for it in a particular formulation.]

It is not possible to list definitively all the excipients used in pharmaceuticals in the United Kingdom (UK) - there are more than 7000 ingredients (including excipients and active ingredients). The following types of excipients have been taken into account in preparing this paper: celluloses, starches and their derivatives; biodegradable and non-biodegradable (including hydrogel) polymers; sodium hyaluronate, sodium chondroitin sulphate and gelatins; dimethicones; polyethylene glycols; preservative macromolecules; ion exchange resins; and natural, synthetic and semi-synthetic gums and thickeners.

REGULATORY REQUIREMENTS

In the United Kingdom pharmaceutical excipients are not approved by the Medicines Control Agency (MCA) in their own right. They are approved as part of a product, for a particular route of administration, dose, and indication. The fact that an excipient has been included in a product approved for one purpose should not be taken as a guarantee that it will be approved for another use.

The regulatory authorities in the European Communities (EC) are guided in their approvals procedures by EC pharmaceuticals Directives, guidance notes and

Table 1
Pharmaceutical Directives

65/65/EEC	78/25/EEC
75/318/EEC	87/18/EEC
75/319/EEC	88/320/EEC
83/570/EEC	86/609/EEC

87/19/EEC

87/21/EEC

87/22/EEC

89/341/EEC

89/342/EEC

89/343/EEC

89/381/EEC

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the Notice to Applicants. European Pharmacopoeia requirements are also to be taken into account, as are national pharmacopoeial monographs and any national guidelines.

The main sources of official requirements in the EC are given in TABLE 1 (Directives), and TABLE 2 (Guidance notes).

Table 2
Notes for Guidance : Quality

Development pharmaceutics and process validation

Chemistry of the active ingredient

Stability tests

Herbal remedies

Analytical validation

Notes for guidance : Biotechnology

Production and quality control of recombinant DNA technology

Production and quality control of monoclonal antibody technology of murine origin

Preclinical biological safety testing

Single dose toxicity studies

Repeated dose toxicity studies

Reproduction studies

Mutagenic potential

Carcinogenic potential

Pharmacokinetic and metabolic studies

Table 2 continued

Clinical guidelines : General

Conduct of clinical trials

Clinical investigations in children

Clinical investigations in the elderly

Pharmacokinetic studies in man

Clinical trials for drugs for long-term use

Fixed combination products

Clinical guidelines : Therapeutic areas

Oral contraceptives

Chronic peripheral artery disease

Chronic NSAIDs

Antiepileptics and anticonvulsants

Corticosteroids

Anti-anginal drugs

Products used in cardiac failure

Anti-arrhythmics

Antidepressants

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The EC pharmaceutical Directives require applications for marketing authorisations to include information on pharmaceutical and chemical, toxicological and pharmacological, and clinical aspects. These will be dealt with in sequence.

PHARMACEUTICAL ASPECTS

Data on pharmaceutical excipients should form part of the dossier to be submitted for a marketing authorisation. In some member states (including the UK) it is possible to submit information in a 'drug master file'.

Much of the information required in the Directives is common to both active ingredients and excipients. A division occurs depending on the availability of a pharmacopoeial monograph for the material. (In this sense 'pharmacopoeial monograph' equates with the availability of a monograph in the European Pharmacopoeia or, in certain circumstances, in the pharmacopoeia of a member state of the EC. The use of a 'third-country' monograph - eg United States Pharmacopeia - must be justified.)

The EC pharmaceutical Directives make it obligatory to require that the standard included in the European Pharmacopoeia (Ph Eur) be applied. Any standard of a member state's pharmacopoeia may be applied if there is no Ph Eur monograph. Where the material has been prepared by a method likely to result in impurities, etc, not controlled by the pharmacopoeia it is necessary that those impurities be declared, a method of control described and maximum tolerance levels stated. In this case the national

authorities may require a specification that is more appropriate to the material in question, and should advise the pharmacopoeial authorities of the deficiency in the monograph concerned.

Where the material is not the subject of a pharmacopoeial monograph it will be necessary to provide rather more information. This will include details of the name of the material (using international non-proprietary names, scientific designations, etc), a description of the material (along Ph Eur lines), the molecular structure of the material (and supporting evidence for this), and sufficient detail of the route of synthesis or preparation to characterise the material.

Suitable routine identity tests should be described. In addition, suitable purity controls should be proposed taking into account factors related to side reaction products, other impurities, related substances, catalyst residues, reagent residues, and solvent residues. Appropriate account should be taken of any impurities that could be clinically harmful, affect stability, or distort analytical results.

Depending on the material and its intended uses the specification may need to include performance tests which will ensure batch-to-batch consistency. Physical characteristics such as polymorphic form or particle size may need to be taken into account .

Specifications should also include a suitable, validated assay.

It is worth emphasising that the marketing authorisation application or its supporting data should

include sufficient description of analytical methods to permit them to be repeated by or for the regulatory authority. Adequate validation of the methods should also be supplied. The nature of the data required may well depend on the intended use of the finished product.

Batch analyses of recent consecutive production-scale lots of the material may need to be supplied. It is helpful if these can include numerical values for test results rather than statements such as 'conforms'. Where toxicity data are required the analyses of the batches (including details of the nature and levels of impurities) used in the pre-clinical studies should be supplied.

The adequacy of the information supplied should be one of the factors discussed in the pharmaceutical expert report that must be submitted with any marketing authorisation application.

The next area of the application that might require special consideration is the manufacture of the dosage form. Where the incorporation of the excipient is a key factor in the satisfactory performance of the product the addition stage should be carefully described and perhaps process validation data provided. An example might be in the incorporation of a low-concentration high-potency drug in a direct compression tabletting formulation where factors such as disaggregation may be importance and where additional controls might be required on the particle size of the ingredients and the content uniformity of the product.

Where the drug is incorporated into the excipient as in the case of a matrix impregnated with drug an

adequate description of the manufacturing process and its validation may also be required.

In terms of the finished product specification some thought should be given to the requirements that could be expected in relation to the incorporation of a particular excipient. Some control tests to ensure consistency of performance might be appropriate. The need for the finished product to comply with Ph Eur general monograph requirements should be borne in mind, as should any specific requirements in individual member state's pharmacopoeias.

The Directives make specific mention of the need to consider tests to at least characterise some types of excipient. Thus, an upper limit should be applied to preserving agents (in the UK lower limits would also normally be expected); an upper limit should also be applied to any material which might affect physiological function; a test should be available to confirm the identity of any colours present; and upper and lower limits should be included for any material liable to affect the bioavailability of the active ingredient(s).

Where an excipient is novel to the pharmaceutical field it will be necessary to consider the provision of stability data on the raw material as well as the finished product.

TOXICOLOGICAL AND PHARMACOLOGICAL ASPECTS

It is indicated in the Directives that an excipient used for the first time in the pharmaceutical field shall be treated like a new active ingredient.

If this is applied fully, data will be required on the following: single-dose toxicity, repeat-dose toxicity, foetal toxicity, reproductive function, mutagenic potential, carcinogenic potential, pharmacodynamics, pharmacokinetics, and in the case of products for topical use information on systemic absorption and local toxicity.

The applicant is expected to review the available data fully . If the material is widely used in, for example, the food industry and has been cleared for such use by an appropriate national or international body, and the intended pharmaceutical usage is by the same route of administration and at the same or lower daily intake, few additional data will be required.

Where the excipient has not been widely used before, a full toxicological package will be required unless a convincing argument can be presented against the need for this. (Such arguments might be based on low absorption and exposure levels, and the pharmacokinetics of the material and its pharmacodynamics, possibly taking into account metabolic breakdown products.)

The route of administration of the product may be very important in relation to the use of an excipient and the data expectations. In the case of many products for oral administration, it is likely that the excipients will be biologically inert or that the gut wall will act as a barrier to their absorption. However, some thought should be given to the degradation products and impurities in the excipients, too.

Products intended for injection routes need special consideration. Those intended for the subcutaneous or intramuscular routes may need to take into account factors such as local osmotic effects and the potential for immunological reactions. Where macromolecules are used in intravenous formulations to solubilise or complex with drugs the potential effects on the kidney and the reticulo-endothelial system should be considered.

Where toxicological studies are required data are frequently available on the excipient tested on its own. These should normally include at least repeat-dose toxicity, reproductive toxicity studies and mutagenicity assessments. Kinetic studies on the combination of active(s) and excipient(s) should be undertaken in addition using radiolabelled active ingredient and radiolabelled excipient, in order to determine whether there is any change in the distribution of either.

Many excipients are added to products in the way of line extensions or reformulations of existing products. As a result inadequate consideration is often afforded the toxicological implications of the changes - for example, of a change from one grade of polyethylene glycol to another, which may involve repeated doses of gram quantities of the excipient.

CLINICAL ASPECTS

The Directives suggest that finished products should be subjected to controlled clinical trials, against either placebo or a relevant comparator of known usefulness. Where possible, the trials should be

double blinded. Trials should be undertaken using the formulation intended for marketing, or good data should be available to demonstrate that any changes to the formulation after the clinical trials will have little or no effect on the safety and efficacy of the product.

The design of clinical trials depends on the condition to be treated as well as the dosage form. There are guidance notes on the conduct of clinical trials in general and also for certain specific therapeutic areas. The choice of excipient may be a contributing factor to some aspects of the trial, but probably will not be the main determinant.

SOME POSSIBLE FACTORS TO CONSIDER

The following notes are thoughts on the types of test that might be of relevance to pharmaceutical controls on macromolecular excipients.

As will have become obvious in the above text, the actual specification that will be considered to be acceptable for an excipient used in one product may differ from that accepted for use in another.

The function of the excipient should be considered as should the intended use of the finished product: this will influence the type and extent of the characterisation tests that will be expected for the excipient. Any testing protocol should aim at confirming the identity of the material as well as its purity and in some cases its potency. The specification should confirm that the material is sufficiently reproducible from batch to batch to allow it to meet its required performance.

It is usual for a specification to cover chemical and physical aspects. Some materials might also require biological or microbiological testing - eg pyrogens tests or bacterial endotoxins limit tests in the case of materials intended for injection; and possibly microbiological counts (especially for materials of natural origin) for materials for other uses. In some cases it might be necessary to consider viral and unconventional organism contamination, too.

Special considerations may apply to materials which have some kind of inherent biological activity.

The method of manufacture of the material may require adequate controls on residues arising from synthesis, including reagents, catalysts and solvents as well as adequate control on impurities and related substances.

Where a macromolecule is being used to modify the rheological properties of a product it would be appropriate to include tests in its specification that would control those properties. This might include molecular weight and molecular weight distribution determinations as well as viscosity controls.

A wide range of modern analytical methods may be applied to the characterisation of macromolecules. The choice of methods will depend on the nature of the material concerned. Some materials may require the routine application of techniques such as gel permeation chromatography, for example where an excipient is not homogeneous and the different molecular weight materials may cause different problems in the formulated product (such as poor compatibility with

antimicrobial preservatives, the formation of coacervates, etc). 'Fingerprinting' may be adequate for some purposes; more detailed specifications for others.

Thermal methods of analysis may be required in certain cases. These include differential scanning calorimetry, differential thermal analysis and thermal gravimetry and may be used to monitor crystallinity, polymorphism and glass transition properties. (They might also be of use in preformulation studies to identify any gross incompatibilities between the various ingredients in a potential formulated product.)

ACKNOWLEDGEMENTS

Thanks are due to many colleagues at the Medicines Control Agency for helpful discussion during the preparation of this paper, including Dr D Jefferys, Dr June M Raine, A C Cartwright, Dr R Lee, and many members of the Pharmaceutical Secretariat.

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Note: The following document should also be taken into account: The Rules Governing Medicinal Products in the European Community, Volume IV, Guide to GMP for the Manufacture of Medicinal Products, ISBN 92 825 9572 2, Office for Publications of the European Communities, Luxembourg, 1989. (9.75 ecu)