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Note

Regulatory issues with excipients☆

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Abstract

The history of the regulatory control of pharmaceutical ingredients is briefly reviewed. The impact of legislation, its interpretation through European and international guidelines and resulting licensing policies are discussed. The important role played by excipients in modern formulations is recognised and some examples are given of the unexpected consequences of inappropriate choices. Some data are provided on the extent to which excipients and active ingredients appear in UK-licensed medicines and on the reference standards (pharmacopoeial and non-official) used to control the excipients. © 1999 Elsevier Science B.V. All rights reserved.

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In recent years, increasing awareness of the properties and roles of excipients in medicinal products has been accompanied by developments in pharmaceutical legislation, regulatory guidelines and licensing policy.

Excipients are all substances contained in a dosage form other than the active substance. Solvents used for the production of a dosage form but not contained in the final product are considered to be excipients (Anon., 1998). The interesting sentence about solvents, though not yet official in the European Pharmacopoeia (PhEur), is compatible with the UK licensing policy that all materials used in dosage form manufacture, even granulation fluids which might be dried off later, should comply to relevant PhEur requirements, unless adequately justified.

Another definition of excipients is "Substances, other than the active drug substance or finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support, enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use" (The International Pharmaceutical Excipients Council, 1995); this definition is more elaborate and alludes to excipi-

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ents having a purpose, which contrasts with the old terminology of 'inactive ingredients' which hints at the property of inertness.

Often in the early 1980s, there was minimal regulatory knowledge about who made the active ingredient or how it was made. Thousands of products had Product Licences of Right, issued for UK medicinal products already being marketed when the Medicines Act became operative in 1972. Industry often treated active ingredients as commodities sourced through brokers and although the buyer must have had a specification this may not have been well known to the licensing authority. Unsurprisingly therefore, regulators knew even less about 'other ingredients', as 'inactive ingredients' became called.

Time did not stand still. To support marketing authorisation (MA) applications, increased information was required on active ingredients. Today, even pharmacopoeial grade may be deemed insufficient for licensing purposes and extra requirements on the control of related substances, residual solvents and residual catalysts are often needed before licensing assessors accept a specification. Other modern demands are to know the name of the manufacturer, the site of manufacture and extensive details about method of synthesis, fermentation, extraction, purification, etc. for each active ingredient. In general, much less information is demanded about excipients.

A recent survey of UK licensing records by the author found 3816 excipients and 2629 active substances in 12 132 current MAs. The high number of excipients is due to the many mixtures of substances, at least 710 colours, 896 flavours, 140 fragrances and perfumes and 24 preservative mixtures being recognised. Standards for excipients are required and provided (mostly house specifications (Fig. 1), largely because of the many proprietary mixtures of colours, flavours, etc.) but often the source and methods of preparation are not demanded.

Excipients may have avoided detailed regulatory attention because it was not always perceived that they have a purpose but nowadays MA applicants are required to state and justify the role an excipient has to play. The desired activity, the excipient's equivalent of the active ingredient's efficacy, is called its 'functionality'.

It is not acceptable to include in a medicinal product an ingredient that is not genuinely needed; a good example is that preservative agents should not be included in a sterile single-dose product (EuroDirect 115/95). A more specific example is that a single-dose injection product should not contain benzyl alcohol as a preservative; however, if benzyl alcohol's role were as a co-solvent for a poorly-soluble active ingredient and this was justified with scientific data, its use would be allowed providing, in this example, the product was contraindicated in infants and children up to 3 years old because of adverse reaction concerns about benzyl alcohol in these target groups.

Genuinely new excipients, those not previously registered with the regulatory authority, are not common, probably because of the requirement in Directive 75/318/EEC (European Commission, 1998a) that an entirely new excipient would have to undergo a full safety evaluation, which would be enormously expensive. More commonly, known excipients are processed to have different physical properties that deliver different functionalities, such as changes in powder flow properties or the ease of compressibility, perhaps because of a change in particle shape.

It has been stated (Armstrong, 1988) that magnesium stearate is the most commonly used excipient. If one discounts water, this is supported by

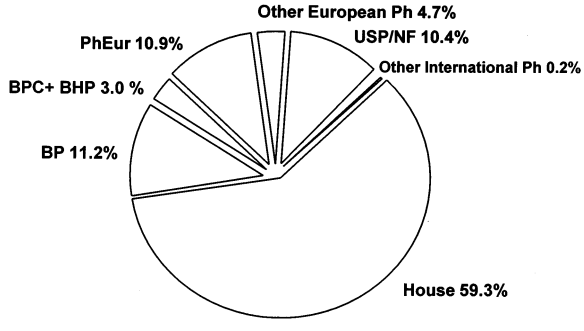

Fig. 1. % Distribution of reference standards for excipients used in UK-licensed medicines. BHP, British Herbal Pharmacopoeia; BPC, British Pharmaceutical Codex; House, non-pharmacopoeial specification; Ph, pharmacopoeia; PhEur, European Pharmacopoeia; USP/NF, United States Pharmacopoeia/National Formulary.

Table 1
Most commonly used ingredients in UK-licensed medicinal products

Ingredient	Times used as an active	Times used as an excipient
Dextrose	279	488
Stearic acid	0	805
Sodium chloride	302	897
Povidone	2	1645
Magnesium stearate	0	4271
Water	51	7100

the author's review of the most common ingredients in UK-licensed medicines (Table 1).

With some exceptions, pharmacopoeial monographs tend not to control functionalities. For example, the Ph Eur monograph for magnesium stearate includes sections on characters, identification and tests but none contain a functionality test (Armstrong, 1988). In such cases, it is for the pharmaceutical development scientist to select a special grade or source of material. An example of an 'exception' is the monograph for ethylcellulose which includes a test for viscosity, enabling manufacturers to produce different grades to the Ph Eur standard but with different viscous properties, to allow an appropriate choice to be made for formulation purposes.

Numerous legal requirements affect excipients. For example, preservatives and other constituents liable to affect physiological functions adversely have to be identified and assayed in the finished medicinal product and colouring matters have to be identifiable (Directive 75/318/EEC). Compatibility of excipients with other ingredients may have to be demonstrated in the development pharmaceutics (EuroDirect 155/96) and analytical validation (European Commission, 1998b) sections of the MA application dossier.

An example of the unwanted influence of a solvent is the polymorphic transformation of the 'desired' Polymorph A of tamoxifen citrate to the 'unwanted' Polymorph B when ethanol is used as the granulation fluid in the manufacture of tamoxifen tablets; this does not happen with aqueous granulation.

The potential contribution of impurities to a medicinal product can be at least as great from excipients as from active ingredients as will be seen by consideration of Table 2.

Although in MA applications, more attention currently seems to be paid to residual solvents in active ingredients than in excipients, this seems illogical given that excipients often contribute the greater bulk to the finished medicinal product. Extensive information about controlling residual solvents is available (Anon., 1997; Connelly et al., 1997).

An excipient can be the subject of a 'PhEur Certificate of Suitability' (Council of Europe Resolution, 1998) which can partly and sometimes fully satisfy the data requirements, within a MA application dossier, for that ingredient (European Commission, 1998c).

Excipients often positively influence the stability of the finished product. The demonstration of antimicrobial preservative effectiveness and the specific assay of preservative content are well-known regulatory requirements. Antioxidants can stabilise active ingredients. Co-solvents can sustain bioavailability by preventing crystallisation in parenterals or by being penetration enhancers in topical products.

Instabilities often caused by excipients include changes in tablet hardness, in disintegration, dissolution and bioavailability in oral dosage forms,

Table 2
The origin of ingredient impurities

Process-related impurities (from synthesis/fermentation/extraction/purification)
Related and other substances (starting materials, reagents, solvents, catalysts, intermediates, by-products)
Degradation products
Other impurities
Transmissible Spongiform Encephalopathies (if manufacture involved certain animal materials, e.g. of bovine origin)
Antibiotic residues (process-related impurities?)
Pesticides, herbicides and fungicides
Microbiological organisms and their products (endotoxins/pyrogens, mycotoxins)
Other adventitious contaminants (extractables from packaging, particulates, pest residues)

in colour and other organoleptic properties, and irreversible sedimentation in suspensions. Crystal formation in topical products and aggregation in dry powder inhalers are not uncommon. Loss of adhesion within transdermal patches during storage and crystallisation of sugars damaging inappropriate packaging during product use have sometimes been observed (Robertson, 1996).

Names of excipients and relevant warning statements have to feature in product documentation including the Summary of Product Characteristics (European Commission, 1998d), and in accordance with Directive 92/27/EEC (European Commission, 1998e,f) the labelling and patient information leaflet texts. For parenteral, topical and ophthalmic products, all excipients must be declared on the label whereas for other product classes only those excipients known to have a recognised action or effect need label declaration. In contrast, for all products, all excipients must be stated on the package leaflet.

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