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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON DEVELOPMENT PHARMACEUTICS

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DEVELOPMENT PHARMACEUTICS

Note for guidance concerning the application of Part II, sections A.4 of the Annex to Directive 75/318/EEC, as amended, of the data required for the granting of a marketing authorisation.

1. INTRODUCTION

Pharmaceutical development studies need to be routinely carried out to establish that the type of dosage form selected and the formulation proposed are satisfactory for the purpose specified in the application. They also aim to identify those formulations and processing aspects that are crucial for batch reproducibility and which therefore need to be monitored routinely.

Because of the great variety in active ingredients and dosage forms, this note for guidance is only an illustration of the type of information which has been found useful in establishing the factors which affect quality of a finished product. Individual guidance may be elaborated for specific types of product, following the general principles illustrated in this note. The note has been elaborated primarily for products containing chemical active substances, but may be applicable also to other types of product. In the case of biological products, such as vaccines and blood products, alternative approaches may be appropriate.

2. COMPONENTS OF THE PRODUCT

2.1 Active Substances

2.1.1 Compatibility

The results of compatibility studies of the active substance(s) with the excipients should be provided where appropriate. In the case of fixed combination products, compatibility of the actives with each other should also be addressed.

The results of preliminary stability studies should be provided as supportive data if available.

2.1.2 Physico-chemical Characteristics

Preformulation testing of the active substances may provide useful information.

It may be necessary to consider the physico-chemical characteristics of the active substance(s) in the formulation in relation to the proposed dosage form and route of administration.

Where a physical parameter is demonstrated to be variable and critical for the quality of the product, it needs to be controlled by an appropriate method with acceptance criteria in the active substance specification or by other appropriate means, This may result in additional physical tests for active substances used in specific formulation (e.g. solid dose forms) over and above those for more simple formulations (e.g. solutions) or those tests laid down in a pharmacopoeial monograph.

Examples of physical characteristics which may need to be examined include solubility, water content, particle size, crystal properties etc.:

i) Solubility may affect choice of formulation and choice of analytical method.

ii) Water content can affect other parameters such as crystal properties and particle size, and can influence stability.

iii) Particle size may affect bioavailability, content uniformity, suspension properties, solubility, stability.

iv) Crystal properties and polymorphism may effect solubility, bioavailability or stability.

Clearly, these parameters are inter-related and may need to be considered in combination. Suitable limits for key parameters affecting bioavailability need to be derived from batches of product showing acceptable in vivo performance.

2.2 Excipients and other non-active constituents

The choice and the characteristics of excipients should be appropriate for the intended purpose.

2.2.1 An explanation should be provided with regard to the function of all constituents in the formulation, with justification for their inclusion. In some cases experimental data may be necessary to justify such inclusion e.g. preservatives (cf Note for Guidance "Inclusion of preservatives and antioxidants"). The choice of the quality of the excipient should be guided by its role in the formulation and by the proposed manufacturing process. In some cases it may be necessary to address and justify the quantity of certain excipients in the formulation.

2.2.2 Compatibility of excipients with other excipients, where relevant (for example combination of preservatives in a dual preservative system) should be established. Supporting stability data may be sufficient.

2.2.3 Where novel constituents are used in the manufacture of the product, e.g. a new matrix of a prolonged release preparation, a new propellant or permeability enhancer, full information on the composition and function of the constituent in the formulation of the product should be furnished together with documentation to demonstrate its safety (Part III).

A new substance introduced as a constituent will be regarded in the same way as a new active ingredient and full supporting data required in accordance with the Note for Guidance on Excipients, unless it is already approved for use in food for orally administered products, or in cosmetics for topical administration. Additional data may still be required where an excipient is administered via an unconventional route, or in high doses.

3. FORMULATED PRODUCTS

The therapeutic activity, posology and route of administration of the active substance and the proposed usage of the product should be taken into consideration when designing the formulation of the product.

3.1 Overages

The use of overages in the formulation of medicinal products is a practice which in general terms needs to be discouraged because of the risk of overdosing.

Overages are primarily employed to cover losses during manufacture of active substances or key excipients, i.e. manufacturing overage, and/or during shelf-life i.e. stability overage. These can be distinguished since in the former case there is unlikely to be increased dosage administered to the patient, whereas the stability overage will result in overdosing where batches of product may reach the patient soon after release. The inclusion of any overage should be justified. Large overages (for example in excess of 10%) should not normally be used to cover up inherently unstable formulations - it is better to reduce a shelf life rather than to risk exposing a patient to

excessive doses of a drug. Similarly overages should not be used to cover up imprecise or inaccurate analytical test procedures or sub-optimal manufacturing processes. The introduction of an overage of an active substance into a formulation should always be justified on the grounds of safety and efficacy of the product. It should also be remembered that over dosage may be introduced by the mechanism of delivery, e.g. deposition of a metered-dose inhaled drug in the mouth.

3.2 Physico chemical parameters

a) pH

Evidence should be presented to show that the effect of pH within the range specified in a formulation has been properly investigated. Consideration should be given to the effect of pH on active substances and, where relevant, on the excipients such as antimicrobial preservatives. The pH profile of an active substance may be useful in investigating the bioavailability of products administered by the oral route.

Should such a study show pH dependency any long term effects would need to be investigated during stability studies. Physiological implications of pH should also be addressed. Where it is necessary to control pH within a narrow range the use of buffers may be necessary.

b) Other parameters

Depending on the formulation, such parameters as dissolution and redispersion, particle size distribution, aggregation, rheological properties, etc. should also be considered during pharmaceutical development studies. In the formulation of parenteral products, consideration may have to be given to such factors as tonicity adjustment, globule size of emulsions, particle size and shape as well as changes in crystal form, viscosity and/or syringeability* etc.

3.3 Liquid and Semi-solid Formulations

3.3.1 Components of the formulation

The concentration of key components in the formulation should be shown to be appropriate for their intended purpose by experimental results. These components might be :

- antimicrobial preservatives
- antioxidants
- others including surfactants, solvents, chelators, permeability enhancers, tablet lubricants, release modifers etc.

3.3.1.1 Antimicrobial preservatives may need to be added to multidose products that in themselves are not self-preserving (cf note for guidance on preservatives) but should not usually be added to sterile single use preparations. Consideration should be given to factors such as storage conditions, reconstitution, dilution before use and frequency of opening the pack, in choosing the levels of suitable preservatives. Testing the efficacy of the preservative system should be conducted according to the test method of the European Pharmacopoeia. It is expected that the system will comply with level A criteria unless otherwise justified. The test should be properly validated including the use of appropriate negative and positive controls, and the choice of suitable organisms to demonstrate appropriate antibacterial and antifungal activity.

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* Syringeability can be considered to be the ability of a product to be successfully administered by a syringe and appropriate needle, and this should be clearly demonstrated where appropriate.

Large packs intended for dispensing may require more stringent testing. The testing programme should allow the assignment of an "in-use shelf life" for the product which will subsequently appear on the product literature. This period should be as short as possible especially for products intended to be sterile such as parenteral or ophthalmic preparations.

Longer shelf lives applied to large packs should be justified and may require additional simulated in-use microbial challenge tests as described in the note for guidance on preservatives.

Pack sizes should themselves be carefully chosen to suit the intended purpose and frequency of use. Content of the preservative during shelf life is controlled by the appropriate finished product specification.

3.3.1.2 Antioxidants may be sacrificially degraded during the manufacture or shelf life of the product. The level of such antioxidants should be justified and supported by suitable experimental data, in order to ensure that sufficient activity is maintained throughout the proposed shelf life of the product (including the in-use period).

3.3.2 Compatibility with other products

This is of particular importance for products to be administered intravenously.

Where the data sheet gives instructions for reconstitution and/or dilution before administration, data should be presented to demonstrate physical and chemical compatibility with the recommended diluents and administration apparatus over the recommended or anticipated period of use.

Where it is proposed in the SmPC to mix a product with another specified product prior to administration, full compatibility data should be provided, over the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration.

3.4 Solid dosage forms

The capacity for chemical incompatibilities or instability is clearly less significant in solids than in liquid or semi-solid media. However where the SmPC recommends dilution or mixing of the solid dose forms (for example with drinks) prior to administration appropriate compatibility studies may need to be carried out.

Differing physical properties of active substances and excipients may also lead to uneven distribution and alteration in drug delivery to the target site. Development studies should therefore attempt to address homogeneity and performance characteristics of bulk or unit-solid dosage forms.

3.4.1 Homogeneity

Mixing processes are normally required to ensure even distribution of the active substance. Differences in surface properties, crystallinity, particle size etc. may result in segregation of powders in dry mixes. Homogeneity achieved by the mixing process should be addressed at the development stage and confirmed by validation studies presented in Part IIB of the dossier.

Studies carried out at the development stage can provide a useful prediction of validation protocols applied to large-scale mixing processes. For the unit solid dose form, it is necessary to demonstrate uniformity of distribution both between batches and within a batch since content determination on a mixed sample will not describe the distribution of active substance between individual dosage units. Uniformity is therefore addressed in the finished product specification (part IIE) on a batch by batch basis.

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