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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.

[*] 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.

Routine testing should be supported by development studies, especially for highly potent substances present in low concentration in a formulation.

Although in general terms the practice of administration of half tablets should be discouraged, where such an approach has been justified in the application it is important to demonstrate the maintenance of dosage uniformity within the tablet halves. Breakability test should be used.

3.4.2 Performance Testing

The performance can be considered as an indicator of the delivery of a drug from the dose form to the target site and will depend upon the type of dose form and the route of administration. Release of an active substance from a dose form may be immediate e.g. suppositories, conventional release tablets or modified in some way either by altering rate or site of release (prolonged or delayed release).

Performance monitoring of unit solid dose forms is usually addressed as the disintegration of the preparation and the dissolution of the active substance in a suitable medium.

3.4.2.1 Disintegration Testing

Disintegration testing is normally applied to each finished batch of oral solid dose forms and also to suppositories or at an intermediate stage such as uncoated cores of tablets or other dose forms prior to application of a final coating. Such testing is intended to demonstrate the effective break-up of the solid formulation (performance of the disintegrant) after administration. Since many solid dose forms disintegrate rapidly, an individually validated limit needs to be set, which will be within the limits specified in the pharmacopoeial monograph. Routine performance of a disintegration test may not be necessary if a dissolution test with acceptable discriminatory power is included in the finished product specification. The test procedure should be as described in the Pharmacopoeia.

3.4.2.2 Dissolution

The actual amount of drug liberated from the dose form into an aqueous reservoir in vitro is intended to reflect the in vivo behaviour of the product. In practice in vivo behaviour is dependent on a number of factors making in-vivo in-vitro correlation difficult. Nevertheless the dissolution test provides a useful range of data and the investigation of dissolution characteristics should routinely be applied to all solid dose forms at the development phase. From such studies a decision can be made as to the relevance of the dissolution test to the in vivo behaviour.

The dissolution apparatus used in the testing of both conventional and modified release oral solid dose forms should be one of those described in the European Pharmacopoeia. Where these prove unsuitable other dissolution test equipment could be adopted. However, justification for the use of a method other than that of the European Pharmacopoeia should be provided.

a) Conventional release preparations

Dissolution tests should be performed during development and stability studies in order to establish whether such testing would need to be included routinely in the finished product specification.

b) Modified release preparations

The choice of dissolution test conditions and release rates adopted for assessing batch reproducibility needs to be justified. This should take account of in vivo studies carried out to establish the release and absorption profile of the product and would, if feasible, consist of a study correlating in vitro release rates to in vivo results to allow meaningful standards to be set for in vitro testing.

Such a correlation would be of particular importance for medicinal products containing active ingredients with a narrow therapeutic window.

For further information refer to the note for guidance on testing of prolonged release oral solid dosage forms.

3.5 Other Dose Forms

3.5.1 Transdermal Patches

Transdermal patches are flexible pharmaceutical preparations of varying sizes containing one or more active ingredients, intended for application to unbroken skin to deliver an active ingredient to the systemic circulation.

Such systems are designed to provide a delivery of active substance through intact skin with a constant systemic absorption rate. Drugs intended to be incorporated into transdermal systems require an appropriate combination of physicochemical properties, potency, biocompatibility and clinical need. These properties should be reviewed in the development studies.

In particular, attention should be focused on the matrix reservoir and adhesive materials to exclude the possibility of incompatibility with the active substance. The release characteristics of the active substance from the patch should be determined using appropriately designed diffusion cells, with a relevant and justified membrane barrier for example using one of the tests described in the Ph. Eur "Dissolution test for transdermal patches (2.9.4)".. Transmission rate characteristics may need to be defined in the product specification, at release and end of shelf life.

3.5.2 Pressured Metered Dose Preparations for Inhalation*

The particle size of the drug substance used in suspension formulations and the qualities of the proposed propellant co-solvent and surfactant should be carefully examined in the light of the desired function.

The propellant may interact with the active substance altering the physical/ chemical properties e.g. particle size, solvation, crystal form etc. The combination should therefore be carefully investigated in the development phase.

The formulation parameters which may need to be examined include moisture content and the potential for extractables following interaction with the valve mechanism. The amount of active ingredient delivered from the valve and mouthpiece should be determined together with the uniformity of content between doses. The deposition of the emitted dose using the apparatus described in the pharmacopoeia should be examined taking into account the capacity for deposition of the drug in the priming dose.

* Further guidance can be found for these preparations in the note for guidance "Replacement of CFCs" and in the draft note for guidance "Dry Powders for inhalation" as well as in the respective general monographs of the European Pharmacopoeia.

It may be necessary from this investigation to introduce such parameters into the finished product specification and during the stability studies of the product. Attempts should be made to correlate the results of in vitro testing with those batches showing acceptable performance in in vivo studies. Deposition of the drug in the mouthpiece may also need to be addressed.

3.5.3 Dry powder for inhalation*

These may be either single dose or multidose. Particle characteristics such as size, shape, rugosity and charge may need to be addressed as should the flow properties of the drug - excipient mix. Since the dose delivered may depend upon the air flow rate, this should be investigated both in vitro and in vivo. Attempts should be more to correlate the results of in vitro testing with those batches showing acceptable performance in vivo. Deposition of the drug in the mouthpiece may also need to be addressed. Other parameters which may need to be addressed include - water content of the drug/excipient mix.

4. PACKAGING MATERIALS

The choice of materials for primary packaging should be justified including appropriate considerations for the safety of medical personnel and patients when the product is in use. Appropriate studies should be performed to demonstrate the integrity of the container and closure where necessary taking into consideration the need for child resistant packaging where appropriate or other kinds of seal. A possible interaction between product and container may need to be considered (refer to the Note for Guidance on Plastic Primary Packaging Materials). This applies also to admixture or dilution of products prior to administration e.g. product added to large volume infusion containers.

The choice of primary packaging materials should also taken into account the proposed method of manufacture. In particular, for sterile products, the container should be chosen so as to allow the optimum sterilisation of the finished product (see under Section 5 below).

4.1 Sorption to container

Data should be presented to show that consideration has been given to the possibility of sorption of the active constituent(s) and additive(s) from liquid or semi-solid formulations if relevant to safety and stability. These phenomena are known to occur with rubber closures and with both glass and plastic containers and administration sets. In extreme cases sorption can lead to permeation through the container walls. Studies should be conducted under simulated in-use conditions, for example by examining products at the distal end of an infusion container fitted with an administration device.

4.2 Leaching

Data should be presented to show that there is no significant leaching of any pack component, into liquid or finely divided solid preparations over the shelf life period, where such leaching could give rise to safety concerns.

4.3 Dose reproducibility

If a dosing device is used e.g. dropper pipette, pen injection device etc. evidence should be presented that a reproducible and accurate dose of the product is delivered under testing

* Further guidance can be found for these preparations in the note for guidance "Replacement of CFCs" and in the draft note for guidance "Dry Powders for inhalation" as well as in the respective general monographs of the European Pharmacopoeia.

conditions, which, as far as possible, are relevant for the use of the product by the patient. Special attention should be paid to the correct reconstitution of lyophilisates intow-change cartridges and to the homogeneous resuspendability of suspensions in cartridges following the instructions for use in the patients leaflets. Special attention should be given to the correct reconstitution of lyophilisates in two-chamber cartridges, and to the homogeneous resuspendibility of suspensions in cartridges following the instruction for use in patient leaflets.

5. MANUFACTURING PROCESS

The choice of the manufacturing process should be explained and justified in the development pharmaceutics section. It is necessary to demonstrate that the method chosen is appropriate for the preparation of the dosage using starting materials of the appropriate quality. The process should enable the definition of appropriate specifications such that the quality of the finished product can be assured. In this way process development studies will lay down the basis for the process optimisation and validation requirements. Such studies should address microbiological as well as physical and chemical parameters and identify the needs for appropriate microbial controls on the quality of the product. The development of the manufacturing process is of major importance in the case of biological products.

For those products intended to be sterile (for example parenteral, ophthalmic and sterile topical products) an appropriate method of sterilisation should be chosen and the choice justified. It should be remembered that wherever possible all such products should be terminally sterilised in their final container, using a fully validated terminal sterilisation method using steam, dry heat or ionising radiation as described in the European Pharmacopoeia[*]. If terminal sterilisation is not possible, filtration through a bacteria-retentive filter or aseptic processing may be considered provided it is fully justified on scientific grounds.

Where a choice is made not to utilise a method of terminal sterilisation, as described in the Pharmacopoeia, proper scientific explanation and justification should be provided in the dossier. Such justification might include the demonstration that a given product was heat labile - that is to say that the active substance or some key component of the formulation is shown to degrade significantly under the sterilising conditions applied. However, head lability of a packaging material should not in itself be considered as adequate justification for not utilising terminal sterilisation, for otherwise heat stable products. The use of alternative packaging materials should be thoroughly investigated before any decision to use non-terminal sterilisation process is made.

6. CONCLUSION

The development studies form a vital background on which to ensure that medicinal products are of the quality appropriate to their intended use. A properly designed formulation manufactured in accordance with the principles of GMP using properly validated processes and test procedures should consistently comply with the desired finished product specification. While the development studies are not normally within the control of GMP inspections, they should nevertheless comply with such principles where appropriate.

Properly conducted development studies should ensure that relevant release and shelf life specifications are applied in order that the desired characteristics of the product can consistently be met at release, and throughout shelf life. (cf Note for Guidance "Specifications and Control Tests on the Finished Products").

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[*] European Pharmacopoeia 3rd Edition - Methods of Preparation of sterile products.