DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(11), 1749-1759 (1990)

DEVELOPMENT PHARMACEUTICS AND PROCESS VALIDATION

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Abstract

A resumé is presented of the guideline on the data required under Part I.A.4. of the Annex to European Directive 75/318/EEC covering the choice of composition of a medicinal product, supported by data on development pharmaceutics. The broad areas of development studies cover the function and compatibility of active ingredients and excipients, the development of liquid, semi-solid and solid dosage forms and the suitability of containers.

The guideline aims also to cover general aspects of process validation. The principles laid down in the Guideline are compared with those of FDA guideline on process validation which are much more detailed, but share the same overall aim.

One of the fundamental aims of the regulatory control of medicinal products is to ensure the correct purity, potency and consistency of manufacture of each product according to the quality appropriate for its intended use. While Good Manufacturing Practice is essential for quality assurance, other factors such as product design and development may also influence quality, and therefore must be studied and controlled. With this in mind, the Regulatory Authorities of the European Community have produced a guideline[1] to the types of studies that should be undertaken in the development of a medicinal product, and which should be presented in support of application for marketing authorisation. A properly presented section on Development Pharmaceutics at the beginning of a dossier is extremely useful, if not essential, in explaining the rationale behind a particular product and giving the reviewer a clearer understanding of the data presented in support of product quality.

Quality Assurance of every product must be demonstrated, and validation is the key to its demonstration, put simply, validation is the act of proving that a process works. Thus the manufacturing methods and controls specified in an application should follow on from the development studies, and be based on valid principles. Demonstration of the validity of the manufacturing process should be provided as should the validation of the analytical methods used to control the process and therefore the product. Thus process validation should be seen as being strongly supported on the one hand by development pharmaceutics, and on the other by analytical validation.

DEVELOPMENT PHARMACEUTICS

Introduction

The rationale for a guideline on Development Pharmaceutics emanates from Part I.A.4 of the Annex to the European Directive 75/318/EEC[2] which calls for the explanation of the choice of composition, constituents and containers of a medicinal product "supported by scientific data on development pharmaceutics". Such pharmaceutical development studies are necessary to demonstrate that the type of dosage form selected and the formulation proposed are satisfactory for the intended use of the medicament specified in the application. These studies further aim to identify aspects of formulation and processing which are crucial for batch reproducibility and which therefore must be routinely controlled. The guideline[1] is broadly divided into five main areas as described below.

1. Constituents

The compatibility of the active constituent(s) with any excipients should be demonstrated. Physical characteristics of the active substance(s) such as crystal form, moisture content and particle size may need to be investigated particularly where these have an impact on the finished dose form e.g. the effect of particle size on the bioavailability of a drug. Where such parameters are identified as critical features, then this should be reflected in the specification of the active substance, or controlled in an appropriate manner.

Overages of active substances in a formulation must be properly justified. Such overages may be intended to cover losses during manufacture (manufacturing overage) and/or during the shelf-life of the product (stability overage).

In the case of inactive constituents of a formulation the function of each of these should be clearly defined. Where appropriate the compatibility of the excipients should be established. In the case of unusual constituents used for the first time in a medicinal product, full information on the composition and function of the component should be provided, together with any documentation available demonstrating the safety of the material. A new substance introduced as a constituent will be regarded in the same way as a new active substance, unless it has already been approved for use in food by the same route of administration.

2. Liquid Dosage Forms

The effect of physical parameters on the dose form, for example pH, particle size, rheological properties etc should be addressed. Evidence should be presented to show that the effects of pH variation, within the range specified, has been properly investigated in particular as to its effect on the stability of the active substance and the efficacy of any antimicrobial preservatives.

Particle size or capacity for aggregation may affect dissolution or dispersion, characteristics of a liquid formulation, and therefore bioavailability. Particle size may be important in the case of parenteral products as may toxicity, emulsion globule size, crystal properties etc.

The concentration of any additive(s) such as preservatives, anti-oxidants etc incorporated in the formulation should be shown by experimental results to be optimum for the intended usage. Consideration should therefore be given to such factors as storage, reconstitution, dilution before use and frequency of opening the pack when choosing suitable level(s) of additive(s) and designing tests to establish the efficacy of the preservative system. Large packs intended for dispensing purpose may require more stringent testing. Both antibacterial and antifungal efficacy should be demonstrated and the test should include suitable positive and negative controls. Testing conditions and the results thereby obtained must be reported.

In some cases it may be appropriate to require studies on the compatibility of the formulation with other products. This may be of importance in the case of products intended for intravenous administration, particularly where dilution is required prior to administration, then physical and chemical compatibility with the recommended diluent over the proposed period of use must be established.

3. Semi-solid Dosage Forms

Changes in physical parameters may also affect the properties of semi-solid dose forms. Once again the effect of pH within the specified range should be addressed insofar as it may affect the active substance or the efficacy of the antimicrobial preservative. Particle size or aggregation may affect suspension properties while rheological properties may also have to be considered.

Typical additives such as chemical and antimicrobial preservatives must be shown to be of optimum concentration for the intended usage, bearing in mind such factors as storage conditions and frequency of opening. Preservative efficacy must be demonstrated using appropriate methods.

4. Solid Dose Forms

In the case of solid dosage forms dissolution testing becomes of paramount importance and should always be carried out by the official, pharmacopoeial, methodology (Ph.Eur., USP etc). Where this is not practical, methodology defined in the national pharmacopoeias or non-compendial methods may have to be used but in such cases, full justification for the use of the different methods should be presented. In the case of unmodified release preparations, testing is required during the development phase to ascertain the need for routine testing in the finished product specification or as it effects stability studies. In the case of modified release preparations routine testing is normally required, the choice of dissolution test conditions are release rates adopted requiring justification. A comparison of invitro release rates with in vivo studies can be carried out in an attempt to correlate the two, and assumes particular significance for drugs with a narrow therapeutic window. Where significant changes are made in composition etc. such correlation studies may require repetition.

Homogeneity of the product must be clearly demonstrated. The European Pharmacopoeia requires a test for uniformity of content for highly potent low content preparations. In addition to this requirement the adequacy of any mixing processes in providing this required homogeneity should always be addressed in development studies.

5. Containers

Appropriate studies should be performed to demonstrate the integrity of the container and closure, while due consideration should be given to possible interactions between the container and the product.

In the case of sorption of product constituents to the container or closure, including absorption, adsorption or permeation, the consequent loss of ingredients may have an adverse effect on product safety, efficacy or stability. These phenomena are known to occur with rubber closures and plastic administration sets. Where evidence exists to indicate sorption to administration sets, reference to this fact should be made in the data sheet.

Conversely data should be presented to demonstrate lack of significant leaching of components of the packaging including container, closure or label adhesive into the liquid, semi-solid, or powder preparations during the normal processing and storage periods.

Where a dosing device is included, evidence of reproducible dosing of product should be presented. The test conditions chosen should as far as possible mimic conditions of use of the product.

PROCESS VALIDATION

Validation is a concept much talked about in all areas of quality assurance but may, in practice, be difficult to pin down. Directive 75/318/EEC[2] generally assumes an underlying reliance on valid processing, but does not lay down a detailed approach to such validation. From a regulatory point of view process validation has therefore fallen between inspection of Good Manufacturing Practice and of data submitted in support of applications for product marketing authorisation.

F.D.A. Guideline

The US Food and Drug Administration has tended to adopt a more concerted approach than European Authorities, laying down principles and practices of general applicability to process validation. The FDA guideline on process validation[3] defines validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes".

In general, the FDA guideline divides validation into the "prospective" and "retrospective" options. Prospective validation is intended to apply to studies carried out prior to marketing, while retrospective validation relates to post-production studies. Although the main thrust of the guideline is directed at prospective validation, the two elements should be seen as synergistic rather than mutually exclusive. Together, confidence can be built into a production process based on accumulated production testing and quality control data.

The guideline addresses the requirement for a "validation protocol", defined as "a written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and decision points on what constitutes acceptable tests results". It is important that the right questions are asked and the sufficient replicates are carried out to provide reproducibility. Analysis of replicate runs should allow the definition of upper and lower processing limits. Key areas in the process can thus be identified as those most likely to lead to failure and this has lead to the concept of the most appropriate challenge conditions better known as "worst case conditions".

The key areas described should be monitored, carefully documented and the data over replicate runs collected. This data can be carefully analysed, it variability established, and proposed in-process controls can be examined to see if these are the correct controls which will ensure that finished product specifications are consistently met. Written procedures are necessary for production and process control such that the quality of the finished product is assured. The main elements of process validation can be considered in four key areas as shown in Figure 1.

1. EQUIPMENT	-	Design
	-	Installation
	-	Operation
	-	Calibration
	-	Maintenance
	-	Running adjustments as appropriate
	-	Critical equipment features
2. PROCESS PERFORMANCE	-	Description/definition
	-	Documentation
	-	Identity key stages
	-	Each process to be validated
3. REVALIDATION		
Required if charges in	-	raw materials
	-	packaging
	-	formulation
	-	equipment
	-	processes
Control tests to monitor changes		
Procedures to determine when required		
Extent.		
4. DOCUMENTATION	-	Properly maintained validation programme.
	-	System of process approval and release.
	-	Careful recording of process details - maintenance log.

FIGURE 1

Elements of Process Validation

European Requirements

These emanate from a requirement in Directive 75/318/EEC[2] calling for description of various stages in the manufacturing process in such a way that assessment of any adverse changes in constituent can be made. In particular the Directive[2] requires

PROCESS ENVIRONMENT	-	Heat
	-	Light
	-	Humidity
	-	Oxygen

Other factors which might have an effect on product quality and stability.

PROCESS EQUIPMENT	-	Selection and specification
	-	Correct and consistent operation.
	-	Where more than one kind of equipment used equivalence must be demonstrated.
PROCESS PARAMETERS	-	Time eg mixing, drying, sterilisation.
	-	Rate of change eg. temperature increase, stirring, application of tablet coating.
	-	Non standard methods of sterilisation.
	-	Stages critical for finished product.

Quality should be identified and controlled eg. modified release system controlled to ensure correct bioavailability.

FIGURE 2

Process Validation - EEC Requirements

"experimental studies validating the manufacturing process where a nonstandard method is used or where it is critical for the product". This requirement is amplified in Notice to Applicants[5] where a definition of validation is provided. However, as indicated earlier, opinion has been divided in the EEC in regard to the method of assessment of such validations steps. In many cases it is held to be the remit of the GMP inspectorate while member states would expect to see varying degrees of validation studies presented in support of application for marketing authorisation.

More recently harmonisation of approaches has lead to agreements on process validation requirements in so far as they

effect marketing authorisation, with the result that the guideline on development pharmaceutics[1] has been expanded to include a section on process validation, covering the processing environment, equipment and parameters (Figure 2).

Factors of the process environment such as heat, light, humidity and oxygen may all have an effect on the product quality and stability and would need to be controlled and validated. Processing equipment would center on areas such as the selection and specification of equipment, the correct and consistent operation, and in particular if more than one kind of equipment is used, the equivalence of this equipment must be demonstrated in terms of product quality. Parameters of the actual process itself requiring validation might include time, e.g. during mixing or drying or sterilisation, rate of change e.g. the temperature increase, rate of stirring, rate of application of tablet coating.

Non-standard methods of sterilisation must be adequately validated in terms of the sterility of the finished product. Stages of the process which are critical for finished product quality should be identified and controlled for example, in the case of a modified release system it would be controlled to ensure correct bioavailability. In-process controls which differ from the requirements of the finished product specification would additionally need to be validated.

Further definitions of validation are provided in various Guides to Good Manufacturing Practice as produced by the EC[5], the European Pharmaceutical Inspection Convention (PIC)[6] and also at national level, for example the UK "Orange Guide"[7]. While the wording may vary slightly the single intention is clear to emphasize the importance of validation in Quality Assurance.

CONCLUSION

There is no single approach to validation as with all aspects of Good Manufacturing Practice and Quality Assurance, and general principles only can be applied. Consequently rather than a set of specific instructions, both the FDA and EC Authorities have developed broad non-mandatory guidelines as illustrations of those principles. Thus certain elements of the various aspects of validation studies will be applicable to the majority of

TABLE 1

Characteristics of a compressed tablet formulation

Characteristics	
PHYSICAL	Dimensions, shape, weight, hardness, freedom from defects, markings.
CHEMICAL	Identity of active ingredients, potency, freedom from breakdown products/impurities.
MICROBIOLOGICAL	Freedom from contamination.
PERFORMANCE	Dissolution and absorption (bioavailability) as reflected by disintegration/dissolution testing.

cases, but no single definitive approach is sufficient to cover all.

Although a well-worn phrase, it remains valid that quality cannot be built into a process by testing of the end product alone. Nevertheless, finished product testing provides an essential part of process validation, provided that the correct specification is being applied.

The design of the product and its intended use should be a determining factor in the development of product characteristics and specifications. Thus, all aspects of the product quality which determine safety and efficacy must be taken into consideration. During the research and development phase the product should be carefully defined in terms of physical, chemical, microbiological and performance characteristics as appropriate. These elements can be illustrated for a compressed tablet, in the following table.

The guidelines on Development Pharmaceutics and process validation, are proving to be very useful to all participants in Drug regulatory activities. While drawing attention to areas of quality assurance which are often overlooked, they should assist

manufacturers in self regulation. At the same time development of these guidelines enables a greater level of international harmonisation between the authorities.

Acknowledgements:

The author gratefully acknowledges the support of Mr. A. C. Cartwright and members of the CPMP Quality Working Party, and also of colleagues, past and present, in the National Drugs Advisory Board, in particular Ms. Christl Kloos, for their assistance. Many thanks to Miss Clare McGloin for the typing of the manuscript.

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