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NOTE FOR GUIDANCE ON MODIFIED RELEASE ORAL AND TRANSDERMAL DOSAGE FORMS: *SECTION II (PHARMACOKINETIC AND CLINICAL EVALUATION)*

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MODIFIED RELEASE ORAL AND TRANSDERMAL DOSAGE FORMS: *SECTION II (PHARMACOKINETIC AND CLINICAL EVALUATION)*

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1. INTRODUCTION

This note is intended to provide guidance for the evaluation of Modified Release Oral and Transdermal dosage forms. It should read in conjunction with the Directive 75/318/EEC, as amended, and other pertinent elements outline in current and future EU and ICH guidelines especially those on

- *Investigation of Bioavailability and Bioequivalence*
- *Pharmacokinetic Studies in Man*
- *Investigation of Chiral Active Substances*
- *Investigation of Drug Interactions*
- *The Extent of Population Exposure to Assess Clinical Safety (ICH topic E1A)*
- *Studies in Support of Special Populations: Geriatrics (ICH topic E7)*
- *Dose Response Information to Support Drug Registration (ICH topic E4)*
- *Statistical Principles for Clinical trials (ICH topic E9)*
- *Choice of control group in clinical trials (ICH topic E10)*

as well as in cross-reference with Section I of this document relating to quality aspects of this type of products.

The primary purpose of Section II of this Note for Guidance is to define the studies necessary to investigate the properties and effects of the new delivery system in man and to set out general principles for designing, conducting and evaluating such studies. However, the precise types and number of tests to be performed have to be defined on a case by case basis taking into consideration the intrinsic properties of the active substance, the route of administration, the type of the delivery system and the intended therapeutic indication(s). This guideline only deals with oral formulations from which the active substance is released slower or delayed than immediate release dosage forms and with transdermal dosage forms. However, most items are also applicable to implants and intramuscular /subcutaneous depot formulations. It should be noted that other types of release dosage forms e.g. pulsatile or accelerated release dosage forms are not covered by the current guideline.

Definitions of the different types of release models as well as other terms used in this guideline are given in Annex 2 (see Section I).

2. GENERAL CONSIDERATIONS

2.1 Rationale for development of prolonged and delayed release formulations

The development of a prolonged or delayed release formulation has to be based on a well-defined clinical need and on an integration of physiological, pharmacodynamic and pharmacokinetic considerations.

A prolonged release form may be considered acceptable if the active substance:

- is regarded as effective and safe;
- does not necessitate the repetition of high concentrations in the body and/or of daily “wash-out periods”, to produce and maintain full therapeutic activity;

- has a concentration-response relationship such that a high level of adverse reactions would ensue from the use of an increased active substance content of a conventional dose form and/or can produce the desirable clinical effect with a lower dose in a prolonged release preparation.

Development of a delayed release form may be considered:

- to protect the active substance from the acid environment of the stomach,
- or to protect the stomach from the active substance.
- whenever the active substance is intended to be released in a defined segment of the intestine in order to decrease drug absorption and yield local action.

2.2 Basis of prolonged therapeutic action

The development of a prolonged release dosage form may offer the following advantages over immediate release formulations:

- ♦ Reduced fluctuations in drug plasma concentrations which possibly may result in a more continuous effect and by avoiding high peak concentrations, a reduction of the incidence and/or intensity of adverse events drug reactions
- ♦ A dosage regimen with lower frequency of administration and thereby potentially improvement of patient compliance.

3. APPLICATIONS FOR MODIFIED RELEASE FORMS OF NEW CHEMICAL ENTITIES

If a new chemical entity is developed in a modified release formulation as a starting product, the submitted dossier should contain the appropriate pharmaceutical and chemical data, all necessary data from preclinical studies as well as a complete clinical data package.

4. APPLICATIONS FOR A MODIFIED RELEASE FORMULATION OF A DRUG THAT IS AUTHORISED AS AN IMMEDIATE RELEASE FORMULATION

In this case the applicant has to validate the new formulation by performing the necessary pharmaceutical and chemical tests as well as with appropriate pharmacokinetic, pharmacodynamic and clinical studies. If new indications are claimed for the modified release formulation, clinical studies for all claimed indications should be carried out**.** Toxicological, pharmacological or clinical tests to define the intrinsic properties of the active substance are not required assuming a similar total systemic exposure of drug/metabolites for the modified and immediate release formulations. In the case of new non-active ingredients animal safety studies should be carried out or the lack of it should be justified.

Modified release forms are developed based on the rationale that there is a relationship between the pharmacological/toxicological response and the systemic exposure to the drug/metabolite(s). The aim of the modified release formulation is therefore, in most cases, to reach a similar total exposure (AUC) to drug and/or metabolite(s) as for the immediate release formulation. This does not necessitate that the same nominal doses are given (the modified release formulation may have a different bioavailability).

4.1 Bioavailability studies

The purpose of these studies is to characterise the modified drug formulation *in vivo* by investigating

- the rate and extent of absorption
- fluctuations in drug concentrations
- variability in pharmacokinetics arising from of the drug formulation
- dose proportionality
- factors influencing the performance of the modified drug formulation
- the risk of unexpected release characteristics (e.g. dose dumping)

The studies are based on concentration measurements of the active substance and/or metabolite(s) or, occasionally, in conjunction with determination of an acute pharmacodynamic effect.

The marketed immediate release product of the same active substance (same salt) should serve as the reference product.

The studies should be performed either in healthy volunteers or in patients.

Whenever multiple dose studies are performed it should be demonstrated that steady state has been reached.

4.1.1. Rate and extent of absorption, fluctuation

Rate and extent of absorption from a modified release formulation should be evaluated by comparison with an immediate release formulation following single and repeated dosing. Fluctuations in drug concentrations should be studied following repeated dosing. It should be demonstrated that the modified release formulation has the claimed release characteristics, produces similar or less fluctuations as the immediate release product and comparable total systemic exposure that is acceptable in comparison to that of the immediate release product. The pharmacokinetic parameters of interest are AUC, C_{max} and C_{min} or other means reflecting fluctuation.

4.1.2 Variability

The inter-individual variability of the pharmacokinetic parameters of interest should be compared between the modified and immediate release formulation and the variability of the modified release formulation should not exceed that of the immediate release formulation. It may be valuable to assess the intra-individual variability. This could be achieved by either repeated measurements of the concentration profile at steady state or by performing a single dose study with replicate design.

4.1.3 Dose proportionality

Whenever there are several strengths some investigations on dose proportionality need to be made. The necessary documentation should be based on the intrinsic pharmacokinetic properties of the drug substance.

If the drug substance exhibits linear pharmacokinetic properties it would be necessary to establish similar total exposure between the modified release formulation and the immediate release formulation at one dose level following multiple dose administration.

If a drug exhibits non-linear pharmacokinetics (in the therapeutic plasma-concentration range) it is necessary to compare the modified release formulation and the immediate release formulation at the highest and the lowest dose level following multiple dose administration. In addition, in all cases dose proportionality for different strengths of the modified release formulations should be adequately addressed.

4.1.4 Factors influencing the performance of a modified drug formulation

4.1.4.1 Food

Different modified release formulations of the same drug substance may differ with respect to food interaction. Hence, the influence of food on the bioavailability of oral modified release formulations must be investigated for safety and efficacy purposes.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high fat meal immediately before dosing. For the assessment of food effect besides AUC and Cmax, it may also valuable to compare the modified release characteristics.

If a significant food effect is found, applicant should give a justified dose recommendation with respect to the intake of the product in relation to meals

Possible approaches for the investigation of the effect of food on the bioavailability of modified release forms reflecting the present scientific approach are presented in Annex 1. However, due to the complexity of the food-drug interaction with any particular dosage form a different approach for *in vivo* studies can be accepted if adequately justified.

4.1.4.2 Gastro-intestinal function

If a modified release formulation will be co-administered with drugs affecting gastrointestinal physiology, it is necessary to investigate the performance of the modified release formulation during these conditions. If the modified release formulation is intended for patients with altered gastrointestinal function the modified release formulation should be studied in those patients.

4.1.4.3 Diurnal rhythms

In view of possible day versus night differences it is recommended that the plasma concentration profile is measured over 24 hours at steady state.

4.1.4.4 Site of application

The effect of different sites of application of transdermal delivery systems on the absorption of the drug should be investigated if the application site is not limited to one body area

4.1.5 Other points to consider

4.1.5.1 Unexpected release characteristics (e.g. dose dumping)

If the modified release formulation contains a higher dose compared to the approved immediate release product the possibility of unexpected release resulting in unacceptable higher exposure should be excluded.

4.1.5.2 Special populations

When the modified release formulation is to be used in a specific subpopulation in which the immediate release formulation is not used, pharmacokinetic data should be generated in that population.

4.1.5.3 Pharmacodynamic studies

When the input rate, in addition to the drug concentration, determines the measured pharmacological response, an investigation of a pharmacodynamic effect linked to therapeutic efficacy is recommended, a PK/PD study could be helpful.

4.2 Therapeutic studies

In general it will be necessary to carry out controlled clinical trials. However, in rare cases, if the assessment of concentration-effect relationship indicates that there is a well-defined relationship between plasma concentration (s) of the drug /active metabolite (s) and clinical response clinical trials may be considered unnecessary.

4.2.1 Objectives and Principles

Therapeutic studies are necessary in the majority of cases when:

- the existence of equivalent levels of effect to those obtained with the immediate release form cannot be assumed on the basis of the pharmacokinetic data, or PK/PD data alone.
- there are complications such as pharmacodynamic tolerance
- different therapeutic activity and/or different adverse reactions prove possible.
- specific claims are made

Comparative studies should adequately be designed and conducted to assess the intensity and duration of the therapeutic effect, adverse reactions and possibly the place of the new treatment among those already available on the market for the same indication.

In addition to specific guidelines the following considerations should be taken into account:

In the assessment of the efficacy and safety of certain therapeutic classes it is necessary to measure the effects of the formulation throughout a 24-hour period and particularly at the end of dosage interval.

The different effects of medicinal products having different dose thresholds:

- Therapeutic activity is quantified with reference to the pharmacodynamic or clinical effects normally adopted as criteria for the assessment of efficacy in the concerned therapeutic class.
- In general an extrapolation cannot be made to indications other than those investigated in the trial. However, in rare cases this may be possible if it is appropriately justified by the applicant.
- In rare cases when the prolonged therapeutic activity may alter the safety profile of drug during chronic dosing, safety studies may be required

4.2.2 Studies related to efficacy

4.2.2.1 Trials to show non-inferiority (equivalence)

Clinical trials which compare the modified release form and the immediate release formulation on the basis of equal exposure, may be planned to demonstrate non-inferiority of therapeutic efficacy. For some products, it will be necessary to demonstrate equivalence. In either situation, the design and analysis of the trials should consider the recommendations of ICH E9.

4.2.2.2 Trials to show superiority

When superiority is claimed it has to be proven with clinical trials.

4.2.3 Specific studies related to safety

If a claim is made for fewer systemic adverse reactions for the modified release form; this has to be substantiated. These trials should be planned and conducted as comparative trials where the immediate release product has to be given using the same total exposure as the control treatment.

In the case of transdermal drug delivery systems studies of adequate design are required to investigate

- Cutaneous tolerability, irritation and sensitization
- The potential for producing a phototoxic reaction

5. APPLICATIONS FOR MODIFIED RELEASE FORMS ESSENTIALLY SIMILAR TO A MARKETED MODIFIED RELEASE FORM

Bioequivalence studies of modified release formulations are recommended to be conducted taking into consideration the following:

- ☛ for orally administered products by comparing two formulations (test versus reference) of same pharmaceutical form
- ☛ for transdermal drug delivery systems by comparing the same transdermal design types

If two products differ in release controlling excipients or mechanism but show similar *in vitro* dissolution profiles, using discriminating tests and with the same claim on release characteristics, these products can be considered as belonging to the same category of pharmaceutical form and are considered as essentially similar after establishing bioequivalence.

If two products differ in their release controlling excipients or mechanism and show different *in vitro* dissolution profiles then clinical trials should be considered except in those rare cases when bioequivalence could be demonstrated.

For convenience the following situations can be described for the three release forms (prolonged, delayed and transdermal) for which this guideline is applicable.

5.1 Prolonged release formulations

Prolonged release formulations can be assessed as bioequivalent on the basis of single and multiple dose studies which are designed to demonstrate that:

- the test formulation exhibits the claimed prolonged release characteristics of the reference;
- the active drug substance is not released unexpectantly from the test formulation (dose dumping);
- performance of the test and the reference formulation is equivalent after single dose and at steady state;
- the effect of food on the *in vivo* performance is comparable for both formulations when a single dose study is conducted comparing equal doses of the test formulation with those of the reference formulations administered immediately after a predefined high fat meal. This study should be conducted with the same strength as those of the pivotal bioequivalence studies.

In case of prolonged release single unit formulations with multiple strengths, a single dose study under fasting conditions is required for each strength. Studies at steady state may be conducted

with the highest strength only if the same criteria for extrapolating bioequivalence studies are fulfilled as described in the Note for Guidance for immediate release forms (linear pharmacokinetics, same qualitative composition ect.).

For multiple unit formulations of a medicinal product showing linear pharmacokinetics with multiple strengths a single dose study under fasting conditions on the highest strength is sufficient, provided that the compositions of the lower strengths are proportional to that of the highest strength, the formulations contain identical beads or pellets and the dissolution profiles are acceptable.

Assessment of bioequivalence will be based on AUC_{τ}, C_{max} and C_{min} applying similar statistical procedures as for the immediate release formulations.

Any widening of the acceptance criteria should be established prospectively in the clinical study protocols. They should be justified from a clinical point of view by the applicant.

5.2 Delayed release formulations

Bioequivalence is assessed using the same main characteristics and statistical procedures as for immediate release formulations with emphasis on the delayed release characteristics.

As food can influence the absorption of an active substance administered in an enteric-coated formulation, post-prandial bioequivalence studies are necessary.

5.3 Transdermal Drug Delivery Systems (TDDS)

In this case, the following points should be considered:

- The bioequivalence of a TDDS in comparison to the innovator's product should usually be assessed after single dose as well as after multiple dose administration;
- The site of application for the bioequivalence study should be in the same body area for both test and reference product;
- When the marketing authorisation of multiple strengths is required, bioequivalence study can be performed with the highest strength provided that
  - ✓ exact proportionality in the formulation i.e. the composition is the same ; the strength is proportional to the effective surface area of the patch and if the lower dose strengths can be considered as "partial" areas of the highest dose strength;
  - ✓ there is an acceptable *in vitro* release test
- As patches are often highly variable drug products it is recommended to assess the intra-individual variability and, in particular, to determine the influence of biopharmaceutical performance on this variability by conducting a study with replicate design;
- If TDDS with different release mechanism (reservoir versus matrix) are compared a study using replicate design is required to investigate subject by formulation interaction;
- Finally, both products should demonstrate the same or less degree of local irritation, adhesiveness to the skin, phototoxicity (phototoxic potential), sensitization and similar systemic adverse events profile compared to the reference product;
- Bioequivalence is assessed using the same main characteristics and statistical procedures as for the prolonged release formulations.

6. JUSTIFICATION FOR MODIFIED RELEASE FORMULATIONS

The dossier submitted in support of an application for a marketing authorisation must provide a complete justification of:

- The physical form of the modified release device and the mechanism of the release form;
- The choice of the dosage form, defining the *in vitro* and/or *in vivo* performance of the product;
- The choice of active substance contents per unit of the dosage form;
- The clinical relevance of the new form particularly in relation to the proposed indications and posology.

6.1 The claimed indications

For a given active substance, the indications for the immediate release form may not apply to the modified release form. For example, the modified release form may be inadequate for the treatment of conditions requiring a rapid onset and short duration of action.

Extrapolations to indications other than those investigated in the submitted trials cannot be made.

6.2 The conditions of administration

The conditions of administration of the modified release formulation and, where appropriate, its use in conjunction with an immediate release formulation should be clearly outlined in the following situations:

- At the initiation of treatment;
- When titration is required;
- For maintenance of therapeutic effect;
- In the management of acute conditions;
- In special populations such as the elderly, children, and patients with renal or hepatic insufficiency.

6.3 Potential uses

The following possibilities should be considered:

- The immediate release form is no longer necessary because the modified release form(s) can be used for all treatments in all patients covered by the indications,
- The immediate release form(s) is/are more flexible to use because the low unit content and thus is/are still valuable:
  - when at the beginning of treatment dosage has to be progressively adjusted before the possible replacement of the immediate release form by the modified release form on the basis of an equivalent dose or doses;
  - in the treatment of special subgroups of patients such as children, the elderly and patients with impaired excretory function and /or in the case of certain indications.

It should be clearly stated in the SPC the need to have immediate release forms available in conjunction with the modified release form. In addition the situations and modes of use of the

two forms should be defined so as to avoid new prescribing problems for the physician and the risk of overdosing (or underdosing) for a significant proportion of the treated patients.

Marketing authorisations cannot be granted to an applicant for a modified release form having a single-dose strength if other dosages are necessary to guarantee the therapeutic effect in terms of dose adjustment and to preclude harmful effects under normal conditions of use.

Specific recommendations should be provided to ensure optimum conditions of use (e.g. instructions not to chew or crush tablets etc.).

APPENDIX 1

RECOMMENDED TRIALS TO STUDY THE EFFECT OF FOOD ON DRUG ABSORPTION FROM MODIFIED RELEASE ORAL DOSAGE FORMS