

# CLINICAL TESTING OF PROLONGED ACTION FORMS WITH SPECIAL REFERENCE TO EXTENDED RELEASE FORMS

<b>Guideline Title</b>	<b>Clinical Testing of Prolonged Action Forms with Special Reference to Extended Release Forms</b>
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# CLINICAL TESTING OF PROLONGED ACTION FORMS WITH SPECIAL REFERENCE TO EXTENDED RELEASE FORMS

## 1. INTRODUCTION

This note for guidance is mainly devoted to extended release forms intended to ensure a more prolonged action and should be read and interpreted in the light of Directive 75/318/EEC as amended.

The primary purpose is to define the studies to be conducted in man, which are specific to new extended release forms containing recognised active and safe medicinal substances so as to ensure a more prolonged action than the conventional pharmaceutical forms already marketed. This note refers predominantly to solid oral forms, but may also apply to forms corresponding to other routes of administration, such as parenteral (sub-cutaneous or intramuscular) or local (transdermal, etc.) routes, intended to develop a systemic effect.

For those new forms containing well-known substances:

- it is inappropriate and unnecessary to repeat the toxicological, pharmacological or clinical tests designed to define the inherent properties of the active substance;
- however, it is insufficient to submit the abridged dossier applicable to medicinal products which are essentially similar to products already marketed (Directive 87/21/EEC) and presented as conventional non-modified forms.

It is necessary to investigate the properties and effects of the new delivery system. This document sets out general principles for conducting such studies in man; the precise types and number of tests to be performed have to be defined on an individual case by case basis as a function of the nature of the active substance, the route of administration, the type of delivery system and the pursued therapeutic indication(s).

## 2. BACKGROUND INFORMATION

### 2.1 Bases of prolonged therapeutic actions

The therapeutic effect of many substances presented in conventional immediate-release pharmaceutical forms is frequently brief or relatively brief.

Although a simple increase in the unit of content of the active substance is generally sufficient to prolong the action, it is also associated with high blood/plasma concentration peaks which are often responsible for an unacceptable level of adverse reactions. As a result, it becomes necessary to change the mode of release and to have recourse to extended release forms except in those rare cases where the active substance does not produce marked dose-related adverse reactions.

## 2.2 Definition of extended release forms

In this document, disregarding the pharmaceutical basis of the type of dosage form, an extended release form is considered as a modified pharmaceutical form of which the release of the active substance and its subsequent absorption are prolonged in comparison with a conventional non modified form. It should be mentioned that the designation “extended release” is used here for the sake of simplicity to cover the above defined general mode of release for which other different terms are frequently employed on the basis of allegedly defined characteristics of the release kinetics: slow, gradual, prolonged, continuous, controlled, delayed, retard etc. forms.

The prolonged release of the active substance in man produces a spread of blood/plasma concentration as a function of time, with an increased apparent elimination half-life and/or reduction in peaks or achievement of a “plateau”. The staggering of concentrations is accompanied by a prolongation of therapeutic action without any increase, and possibly with a reduction in adverse reactions.

## 2.3 Fields of application

An extended release form can be only considered acceptable if the active substance simultaneously:

- 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 dose 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 an extended release preparation.

Recourse to an extended release form is generally more appropriate if the active substance:

- has a short, or relatively short, intrinsic elimination half-life and/or action,
- is intended for long-term treatment, the reduction in dose frequency being likely to improve compliance of patients.

## 2.4 Objectives of clinical testing

Studies in man have a dual purpose, namely:

- to establish firstly that the new form definitely exhibits extended release in vivo; this is a necessary, though not always sufficient condition for obtaining a prolonged effect;
- and subsequently to verify that a prolonged therapeutic effect is achieved and that the mode of administration makes effective and safe treatment possible.

These two “validation” stages – biopharmaceutical and therapeutic – are dealt with in succession below.

### **3. BIOPHARMACEUTICAL VALIDATION OF THE EXTENDED RELEASE FORM**

The *in vivo* performances of extended release forms are generally studied after the administration of a single dose to healthy subjects on a comparative basis, taking as a reference preparation conventional forms administered by the same route (marketed conventional forms, solution or suspension prepared extemporaneously) and/or by another route of administration or a different form (e.g. intravenous perfusion and/or ointment in the case of a transdermal system). Unless otherwise justified, studies should also be performed at steady state, after repeated administration in patients or in healthy volunteers.

These bioavailability studies are mostly based on the determination of pharmacokinetic parameters, though they occasionally make use of biological or pharmacodynamic parameters (see the note for guidance on *Investigation of Bioavailability and Bioequivalence*).

It is necessary to define the dosage form delivery system in terms of its rate and extent of substance delivery as well as its reproducibility.

#### **3.1 Rate of delivery**

Analysis of the profile of blood/plasma concentrations, particularly of the maximum concentrations ( $C_{max}$ ) and the time of their appearance ( $t_{max}$ ) and, for instance, of the duration of release estimated by the mean resident time (MRT), makes it possible to evaluate compatibility with the attainment of a prolonged effect.

#### **3.2 Extent of delivery**

Poor bioavailability may lead to an unacceptable dose-form insofar as it is likely to reduce the level of activity significantly or to increase inter-subject fluctuations unacceptably. For active substances with a low therapeutic index, the bioavailability of the extended release form should be close to that of the conventional form.

In the case of transdermal forms, the extent of absorption is evaluated not solely with reference to both the blood/plasma or urine concentrations, but also taking into account the residual quantities of the active substance present in the product after the removal of the delivery system applied to the skin.

#### **3.3 Reproducibility of *in vivo* performances**

Variability between or within subjects significantly greater than that found using the conventional form should be taken into account in assessing the extended release forms and may constitute a possible reason for the new dose-form to be deemed unacceptable.

#### **3.4 Special characteristics to be determined in the case of certain extended release forms**

It may be necessary to study the influence of:

- diet, in the case of orally administered forms, for example to determine whether dose-dumping occurs. Where necessary, the influence of the nature of the diet and of the related changes of gastric pH should also be studied;
- the sites of application, in the case of forms applied to the skin.

If for an extended release form there are several differing dosages as regards product surface area and/or unit content, it is necessary to establish that these different presentations give identical in vivo and/or in vitro performances.

#### **4. MEDICINAL RATIONALE: THERAPEUTIC VALIDATION OF THE EXTENDED RELEASE FORM**

These studies are designed to establish that forms which are satisfactory from the biopharmaceutical standpoint (see item 3) make it possible to attain the therapeutic objective in question in accordance with a particular mode of administration (dose levels and frequency):

- therapeutic activity must be maintained for the entire dosage interval between two administrations and overall for the duration of treatment; the intensity of activity is usually equivalent to or above that obtained with the conventional form; it must always be sufficient to justify the claims made with regard to indications;
- the nature, extent and frequency of adverse reactions must not cast doubt on the value of the treatment; they must be globally equivalent or inferior to those produced during treatment with the conventional form;
- any claims as to an improvement in compliance should be duly justified.

Pharmacokinetic and clinical studies should be conducted after repeated administration to patients exhibiting the stated indications. Depending on the indication(s), the influences of age, renal or hepatic impairment should be analysed.

##### **4.1 Pharmacokinetic studies**

These are conducted whenever possible and involve comparison of the extended release form with the conventional reference form at the steady state with regard (inter alia) to  $C_{max}$ ,  $C_{min}$ , A.U,  $t_{max}$  and their fluctuations.

4.1.1 The principal objective is to verify and extend, under the recommended conditions of administration, the patient data already obtained concerning the in vivo performance of the extended release form; apparent differences in bioavailability observed after a single dose may cease to be significant at a steady state.

4.1.2 Another objective can be to establish, by inference from the blood/plasma concentrations obtained with the extended release form, that the levels of therapeutic activity and adverse reactions are equivalent to those of the reference form. Such an assumption can be made if:

- a) the blood/plasma concentrations as a function of time are considered to be globally similar (equivalent) with the two forms,  
and/or
- b) they are situated in the therapeutic range, that is in the zone of concentrations which are generally directly associated with adequate therapeutic efficacy and the absence of marked adverse reactions.

Clinical studies may then be considered unnecessary, particularly in situation (b) where a direct relationship is recognised between plasma levels and therapeutic activity (e.g.

quinidine, theophylline, ...). Nevertheless, it is useful, whenever possible, to verify the persistence of activity at the end of the dosage interval (e.g. anti-arrhythmic activity by Holter recording).

In practice, it is rarely possible to predict levels of therapeutic efficacy and/or adverse reactions from blood/plasma concentrations, since:

- a therapeutic range is not known in the case of most active substances;
- the profiles of blood/plasma concentrations against time show usually an unacceptable difference for the two forms, the extended release forms producing fewer and lower peaks than conventional forms, so that the assumption (a) cannot generally be made.

## **4.2 Therapeutic Studies**

### ***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 conventional form cannot be assumed on the basis of the pharmacokinetic data (see item 4.1);
- different therapeutic activity and/or different adverse reactions prove possible.

Studies – generally comparative – should be conducted to evaluate the intensity and the duration of the therapeutic effect of a single dose and as a function of one or more dosage schedules involving multiple administration, the overall effectiveness of the treatment, adverse reactions and, possibly, the place of the new treatment among those already available on the market for the same indication. Studies should be designed and performed in order to take into account the following considerations:

- a) there is a need to assess therapeutic efficacy and adverse reactions as a function of time during the complete daily cycle (24 hours) and, more particularly, at the end of dosage intervals; the possibility of development of a rapid tolerance should also be explored. The comparison should also consider what dosage regimen of the conventional forms could be replaced by the new forms.
- b) 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;
  - an extrapolation cannot be made necessarily from one therapeutic indication to another.
- c) in the case of products intended for prolonged or life-long use, courses of treatment lasting several months are necessary in order to evaluate the maintenance of efficacy, safety and compliance.

### ***4.2.2 Studies related to efficacy and safety***

Four different approaches, which are not mutually exclusive, are described below. Comparison with the standard treatment involving a validated conventional form or comparison with a placebo are the two main approaches which may be followed (see items (a) and (b)). However, comparison with other recognised active substances or with a dissimilar

validated extended release form are two other possible types of study which may be performed (see items (c) and (d)).

a) Comparison with the standard treatment involving a validated conventional form:

- Comparison between the two forms, generally on the basis of equal doses, is intended to demonstrate the equivalence or superiority of the extended release form; this approach is not without difficulties and presents the following disadvantages:
- demonstration of therapeutic equivalence will require the study to be sufficiently powerful to result in narrow confidence intervals for the difference or ratio of outcome measures using the two forms (and not just absence of a significant statistical difference).
- demonstrated equivalence relates solely to the dosage studied.

b) Comparison with a placebo:

Comparison with a placebo is particularly useful as a means of:

- demonstrating therapeutic efficacy unambiguously, given the difficulty of showing therapeutic equivalence to an active treatment,
- determining the duration of therapeutic action following a single dose and/or repeated administration,
- assessing exactly the importance of adverse reactions.

c) Comparison with other recognised active substances:

It may be advantageous, and even necessary, to compare the extended release form with other active substances which are known to be safe and effective, particularly in the case of an important innovation associated with the mode of administration, in order to assess the new product with respect to conventional treatments (e.g. glyceryl trinitrate or clonidine transdermal systems).

d) Comparison with a dissimilar validated extended release form:

The foregoing remarks on the difficulties of demonstrating the therapeutic equivalence of two forms (see (a) above) also apply in this case.

#### ***4.2.3 Specific studies related to safety***

Safety should be considered both in terms of systemic adverse reactions and of local irritation or sensitisation and may require additional clinical testing for safety in patients.

Unless it has already been assessed during the above-mentioned studies, additional studies of systemic adverse reactions must be conducted under normal conditions of use; this should be especially considered when less adverse reactions are claimed for the new form.

Specific studies of local adverse reactions will also cover the delivery system with and without an active substance.

## **5. PARTICULAR CASES OF OTHER FORMS INTENDED TO ENSURE A PROLONGED ACTION**

According to the primary goal of this note for guidance, the previous sections were dedicated to new extended release forms containing well-known active substances and having a more prolonged action than the conventional forms already marketed. For the sake of completeness, this section deals briefly with other types of pharmaceutical form.

### **5.1 New high-dose conventional dosage form**

These dosage forms are not prolonged action forms; nevertheless, like extended release forms, they enable less frequent administration; consequently, similar studies to those laid down for the validation of extended release forms must be conducted, comparison with the standard-dose conventional form being essential to justify the new conditions of administration.

In view of the extent of blood/plasma peaks, special attention should be given to the investigation of adverse reactions.

### **5.2 Extended release form, essentially similar to a marketed, validated form**

The equivalence of the in vivo performances of the extended release forms must be demonstrated.

Acceptability studies are to be conducted where necessary; thus, the local tolerance of a transdermal system which is essentially similar to a marketed validated system must be studied, since – apart from the active substance - the constituent materials of the delivery system applied to the skin may be different and cause local irritation or sensitisation.

### **5.3 New active substances presented from the beginning in an extended release form**

The standard efficacy and safety tests applicable to all new medicinal products should be conducted in man; nevertheless, the recommendations made in this note for guidance concerning the justification and validation of the pharmaceutical form and its condition of administration also apply fully.

## **6. JUSTIFICATION OF THE PROLONGED ACTION FORMS**

It is useful for the dossier to indicate:

- the clinical interest of these new forms,
- and, especially in the case of these new forms, the amount of therapeutic progress achieved, linked at least with the reduction to a greater or lesser extent of the number of doses taken, simplification of treatment and possibly new indications, a reduction in adverse reactions, increase in activity and improvement in patient compliance. Proper evidence must be given for the benefits claimed.

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

- 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.

## **6.1 The claimed indications**

For a given active substance, the indications for an extended release form are not automatically the same as those of the conventional forms; they may be different, thus opening up a new field of application (e.g. nitrate derivatives), or fewer in number than those of the conventional forms so that:

- the extended release form may be inadequate for the treatment of conditions requiring a rapid and short action;
- an automatic extrapolation cannot be made from one indication to another.

## **6.2 Conditions of administration**

6.2.1 It must be made quite clear in the dossier whether or not the extended release form or its various dosages can be used:

- at the initiation of treatment at a fixed dose or with a gradual increase in the dosage, in spite of a high unit dose and/or delayed action,
- for initial treatments with one or several loading dose(s) and for acute attacks,
- for maintenance treatment(s) covering the whole range of doses normally used,
- for the treatment of special patients exposed to greater risk such as children, the elderly and persons suffering from renal or hepatic insufficiency.

Two possibilities should be considered when this balance sheet of potential uses has been compiled, namely:

- a) whether the extended release form(s) can be used for all treatments in all patients covered by the indications, in which case the conventional form is no longer necessary;
- b) or because the low unit content makes the conventional form(s) more “flexible” to use, they are/it is still valuable:
  - when dosage has to be progressively adjusted at the beginning of treatment before the possible replacement of the conventional form by the extended release form on the basis of an equivalent dose or doses;
  - in prolonged treatments where the specific doses are different from that or those studied in the dossier on the extended release form;
  - in the treatment of specific types of patients: children, the elderly, those suffering from renal failure etc. and/or in the case of certain indications.

The need to have conventional forms available in conjunction with the extended release form must be made clear in the information provided, which must define as clearly as possible the situations and modes of use of the two forms so as to avoid new prescribing

problems for the physician and the risk of overdosing (or underdosing) for a significant proportion of those treated.

6.2.2 Marketing authorisations cannot be granted to an applicant for an extended release form having a single unit dosage if other dosages are necessary to guarantee the therapeutic effect in the context of dose adjustment and to preclude harmful effects under normal conditions of use (e.g. theophylline).

6.2.3 The information provided must include specific recommendations aimed at ensuring optimum conditions of use (e.g. instructions not to chew or crush tablets etc.).

### **6.3 It is useful for the dossier to indicate:**

- the clinical interest of these new forms;
- and, especially in the case of extended release forms, the amount of therapeutic progress achieved, linked at least with the reduction to a greater or lesser extent of the number of doses taken, simplification of treatment and possibly new indications, a reduction in adverse reactions, increase in activity and improvement in patient compliance and disease control. Proper evidence must be given for the benefits claimed.

## ANNEX

Terminology for this class of medicinal products is still not very standardised. Below is a table listing several kinds of modified release products and a proposed terminology. The classification has been based on pharmacokinetic criteria.

### Subclasses of Modified Release Products

Name	Plasma concentration peak	Elimination half-life
Slow Release:	lower $C_{max}$ , later $t_{max}$	$t_{1/2}$ unchanged
Extended Release:	lower $C_{max}$ , later $t_{max}$ , $t_{max}$ often III defined	apparent $t_{1/2}$ appreciably longer than intrinsic $t_{1/2}$
Delayed Release:	$C_{max}$ unchanged, lag time	$t_{1/2}$ unchanged

Slow release product may be useful in preventing or minimising plasma concentration related adverse reactions, using the same dosage scheme.

The extended release allows the adoption of a dosage scheme with less frequent dosing. As absorption kinetics of these products may approach infusion kinetics (zero order absorption),  $t_{max}$  often is III defined: plateau or multiple peaks. Because of the long absorption half-life, the apparent elimination half-life is determined by the absorption rate.

Delayed release products are designed to release their active substance after a lag time. An example is the enteric coated tablet, which remains intact in the acid stomach environment and which only disintegrates in the intestine after dissolution of a film coating in the neutral environment of the intestine.