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Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)

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This guideline replaces Guideline on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical Evaluation (EMA/CPMP/EWP/280/96 Corr*))

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu.

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Executive summary

The primary purpose of this guideline is to define the studies necessary to investigate the efficacy, safety, biopharmaceutic and pharmacokinetic properties of modified release and transdermal dosage forms in man and to set out general principles for designing, conducting and evaluating such studies. The revision of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (EWP/QWP/1401/98) generated the necessity of consequential adjustments. Furthermore the guideline provides updated requirements for transdermal drug delivery systems (TDDS) and addresses recommendations for specific modified release formulations, e.g. for intramuscular/subcutaneous depot formulations.

1. Introduction (background)

1.1. Types of Modified release and dosage forms

Modified release dosage forms are formulations where the rate and/or site of release of the active ingredient(s) is different from that of the immediate release dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing methods. Modified release dosage forms covered by this guideline include orally, intramuscularly, subcutaneously administered modified release and transdermal dosage forms.

- **Prolonged release dosage forms:** Prolonged release dosage forms are modified release dosage forms showing a slower release than that of an immediate release dosage form administered by the same route.
- **Delayed release dosage form:** The release of the active substance from such modified release dosage forms is delayed for a certain period after administration or application of the dosage. The subsequent release is similar to that of an immediate release dosage form.
- **Multiphasic release dosage forms:**
    - **Biphasic Release:** The first phase of drug release is determined by the immediate release dose fraction providing a therapeutic drug level shortly after administration. The second extended release phase provides the dose fraction required to maintain an effective therapeutic level for a prolonged period.
    - **Pulsatile Release:** Pulsatile drug release is intended to deliver a burst of drug release at specific time intervals.
- **Multiple-unit:** A multiple unit dosage form contains a plurality of units e.g. pellets or beads each containing release controlling excipients, e.g. in a gelatine capsule or compressed in a tablet
- **Single-unit**: The single-unit dosage forms consist of only one unit, e.g. osmotic tablet.
- **Intramuscular/subcutaneous Depot formulations:** A depot injection is usually a subcutaneous or intramuscular product which releases its active compound continuously over a certain period of time. Subcutaneous depot formulations include implants.
- **Transdermal drug delivery systems (TDDS):** A TDDS or transdermal patch is a flexible pharmaceutical preparation of varying size containing one or more active substance(s) to be applied on the intact skin for systemic availability.

There are two main types of transdermal patch systems depending on how the drug substance is dispersed in other patch components: matrix and reservoir systems. Drug release from matrix systems is based on the diffusion of soluted drug substance from the patch. Reservoir systems contain a specific liquid drug compartment and release is controlled by a membrane.

1.2. Rationale for Development

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

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 in vivo performance of the product;
- The choice of active substance contents per unit of the dosage form;
- The clinical rationale for the new dosage form, particularly in relation to the proposed indications and posology.

1.2.1. The clinical rationale

A *prolonged release dosage form* may be acceptable if the active substance can produce the desirable clinical effect with a different PK profile than that resulting from an immediate-release form. A prolonged release formulation may offer the following advantages over an immediate-release form:

- reduced fluctuations in drug plasma concentrations, which may result in more continuous effects and/or reduced incidence and/or intensity of adverse drug reactions,
- lower frequency of administration and thereby potentially improvement of patient compliance.
- non-oral route of administration (IM/SC and TDDS)

A *biphasic modified release form* may be considered if a rapid onset of action is required in addition to subsequent prolonged release characteristics.

Development of a *delayed release dosage form* may be considered to protect the active substance from the acid environment of the stomach, to protect the stomach from the active substance, or when the active substance is intended to be released in a defined segment of the intestine. Delayed release forms are generally not adequate for conditions requiring a rapid onset of action.

Development of a *pulsatile release dosage form* may be considered when treatment needs to be adjusted to a circadian rhythm of the underlying condition or when lower frequency of dosing is desirable, but the fluctuating plasma concentration profile of the immediate-release formulation is necessary for efficacy.

1.2.2. Considerations for use and posology

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. Lack of dose strengths of the modified-release form to cover all required dose levels, e.g. a lower dose for special populations, should be justified.

When appropriate, recommendations should be given for switching between immediate release and modified release formulations. If applicable, specific recommendations should be provided to ensure optimum conditions of use (e.g. instructions not to chew or crush tablets etc.).

2. Scope

This guideline is to define the studies necessary to investigate modified release drug delivery systems in man and to set out general principles for designing, conducting and evaluating respective 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). The guideline deals with oral formulations, intramuscular depot formulations, subcutaneous implants, and transdermal dosage forms containing chemically defined drug substances.

Separate guidance and standards are required for each of the circumstances in which an MR formulation might be developed. These circumstances fall into three groups:

- Applications for modified release forms of new chemical entities (NCE)
- Application for a modified release formulation of a drug that is authorised as an immediate release formulation
- Abridged applications for modified release forms referring to a marketed modified release form, e.g. applications according to Article 10(1) or 10(3)

For generic prolonged release or delayed release products this guideline provides requirements on bioequivalence studies that are not covered by the current guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the Annex I of Directive 2001/83/EC as amended, as well as European and ICH guidelines for conducting clinical trials, including those on:

- General considerations for clinical trials (ICH E8, CPMP/ICH/291/95)
- Guideline for good clinical practice (ICH E6 (R1), CPMP/ICH/135/95)
- Statistical principles for clinical trials (ICH E9, CPMP/ICH/363/96)
- Structure and content of clinical study reports (ICH E3, CPMP/ICH/137/95)
- CHMP guidance for users of the centralised procedure for generics/hybrid applications (EMEA/CHMP/225411/2006)
- Pharmacokinetic studies in man (Eudralex, Volume 3, 3CC3a)

- Quality of oral modified release products (EMA/ 492713/2012)
- Guideline on quality of transdermal patches (EMA/CHMP/QWP/911254/2011)
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)
- Fixed combination medicinal products (CPMP/EWP/240/95)
- Note for Guideline on the investigation of drug interactions (CPMP/EWP/560/95)
- Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)
- Clinical investigation of medicinal products in the paediatric population (ICH E11, CPMP/ICH/2711/99)
- Studies in support of special populations: geriatrics (ICH E7, CPMP/ICH/379/95) and Questions and Answers - EMA/CHMP/ICH/604661/2009

The guideline should also be read in conjunction with relevant guidelines on pharmaceutical quality. The test products used in the bioequivalence study must be prepared in accordance with GMP-regulations including Eudralex volume 4.

Clinical trials, including bioequivalence and pharmacokinetic studies, conducted in the EU/EEA have to be carried out in accordance with Directive 2001/20/EC. Trials conducted outside of the EU and intended for use in a Marketing Authorisation Application in the EU/EEA have to be conducted to the standards set out in Annex I of the community code, Directive 2001/83/EC as amended.

4. Applications for modified release dosage forms of new chemical entities

If a new chemical entity is developed to be administered as a modified release dosage formulation, the submitted dossier should contain the appropriate pharmaceutical and chemical data, necessary preclinical studies and a complete clinical data package as for any full application.

4.1. Pharmacokinetic studies required for MR formulation of a new chemical entity

A complete pharmacokinetic data package is required for a new chemical entity developed as MR formulation. Additional documentation specific to the MR dosage form include studies evaluating factors affecting the biopharmaceutic performance of the modified release formulation (see section 5.1.4 and 5.1.5).

In order to avoid a duplication of studies (e.g. time and dose dependency), it is advisable to conduct PK studies with the MR formulation as early as possible during clinical development. Initial phase I studies (e.g. first in man studies) are generally conducted with an oral solution or an immediate release formulation where basic pharmacokinetic characteristics of an active substance (T_{max}, Vd, Cl, elimination half life, route(s) of excretion) are obtained. Interaction studies and studies in special populations should preferably be conducted with the modified release formulation. In addition to general pharmacokinetic investigations relevant to any new formulation (e.g. single and multiple dose PK parameters, food effect when relevant and dose proportionality), the mechanism for the control of drug release should be described. This is generally done through bioequivalence/relative bioavailability studies conducted using different formulations where, for instance, the amount of a release controlling

excipient varies if possible. The obtained pharmacokinetic profiles in vivo are recommended to be correlated with in vitro drug release profiles if possible (see Appendix II).

4.1.1. Food effect studies with oral modified release forms

Food interactions may be related to the drug substance itself and/or the formulation, the latter being most important in the case of modified release (MR) products.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high fat meal immediately before dosing (see section 5.1.4.1).

Food effect studies for new MR formulations are recommended to be conducted early during drug development so that appropriate recommendations regarding intake in relation to food can be included in clinical efficacy and safety studies. This is also important from safety perspective as the risk for dose dumping should be evaluated before initiation of efficacy and safety studies.

To evaluate the influence of food on the absorption of the drug substance from the new formulation a 2-way cross over study (MR formulation fasting and fed) may be sufficient. If there is a food effect on the MR formulation additional study(ies) with an oral solution can be considered, to evaluate if the food effect is related to the formulation or to the drug substance. In this situation, a single dose 4 way crossover study; MR fed and fasted + oral solution (or immediate release (IR) formulation if a solution is not feasible) fed and fasted can be conducted.

In case there is a marked food-effect, additional food-interaction studies might be needed to support dosing recommendations, i.e. studies of the effect of different kinds of food, studies investigating the effect of a meal taken at certain time period before and after the drug, etc. (see Note for Guidance on the investigation of drug interactions (CPMP/EWP/560/95)).

4.2. Pharmacokinetic Studies required for Transdermal Drug Delivery Systems (TDDS) of a new chemical entity

If a new chemical entity is developed to be administered as a TDDS formulation, the submitted dossier should contain the appropriate pharmaceutical and chemical data and a complete non-clinical and clinical data package as for any full application.

Generally, the kinetics of drug delivery from TDDS' is determined by the interplay between the active substance, the formulation and the skin. Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or skin reservoir and/or other formulation related particularities. Pharmacokinetic investigations should comprise single-dose and multiple-dose investigations considering particular aspects like e.g. application site-dependent absorption, fluctuation, lag-times and concentration time profile after patch removal. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose proportionality issues should be adequately addressed.

In addition to conventional phase I studies skin irritation, sensitisation (see also appendix 1), phototoxicity, patch adhesion and, in general, the effect of sauna and sun cream on the patch adhesion (see also Guideline on quality of transdermal patches EMA/CHMP/QWP/911254/2011) should be investigated.

4.3. Pharmacokinetic Studies required for intramuscular/subcutaneous Depot formulations of a new chemical entity

Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or other formulation related particularities. Pharmacokinetic investigations should comprise single-dose and multiple-dose investigations considering particular aspects like e.g. application site-dependent absorption, fluctuation and lag-times. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose proportionality issues should be adequately addressed.

5. Application for a modified release formulation of a substance that is authorised as an immediate release formulation

Modified release forms are developed based on the rationale that there is a relationship between the pharmacological/toxicological response and the characteristics of systemic exposure to the active substance/metabolite(s). The aim of the modified release formulation is therefore, in most cases, to reach a similar total exposure (AUC) to active substance 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 extent of absorption).

In general modified-release formulations are not bioequivalent to their immediate release form. Consequently PK data alone may not be sufficient for evaluating whether the benefit/risk ratio of the modified release formulation is comparable to the corresponding doses of the immediate release form. Therefore additional clinical data will generally be required.

Whenever the strength of the new modified release formulation differs from those approved for the immediate release product this difference and the possible resulting different dosage regime has to be highlighted very clearly in SmPC, PL and labelling as most important routine risk minimisation measures to avoid medication errors. The applicant has to prove that the benefits of the new formulation outweigh the potential risks linked with this product.

The new formulation should be characterised in appropriate pharmacokinetic, pharmacodynamic and clinical efficacy/safety studies. Recommendations regarding pharmacokinetic studies to characterise the formulation is given in section 5.1 and the need for therapeutic studies in section 5.2. Additional studies may in certain cases be needed, e.g. pharmacokinetic studies to characterise the metabolic profile may be required in case the modified release product is administered by a new route of administration.

Toxicological, pharmacological or clinical tests to define the intrinsic properties of the active substance are not required assuming a similar total systemic exposure of active substance/metabolites for the modified and immediate release formulations.

The marketed immediate release product of the same active substance should serve as the reference product. The final market formulation should in general be used in the pharmacokinetic and therapeutic studies, unless it can be justified that differences between the study formulation and final market formulation do not affect release characteristics and bioavailability.

5.1. Pharmacokinetic studies

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

- the rate and extent of absorption
- fluctuations in drug concentrations at steady state
- inter-subject variability in pharmacokinetics arising from the drug formulation
- dose proportionality
- factors affecting the performance of the modified release 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 studies can 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. In case of no accumulation (i.e. insignificant levels at the end of the dosing interval) multiple dose studies are not required since steady state is achieved after a single dose.

5.1.1. 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 dosing and generally also repeated dosing.

The pharmacokinetic parameters of interest may be for single dose studies $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max} , t_{max} and t_{lag} and for multiple dose studies $AUC_{(0-\tau)}$, $t_{max,ss}$, $C_{max,ss}$, $C_{min,ss}$ and fluctuation. The pharmacokinetic parameter(s) chosen as primary for the comparison, i.e. the parameter(s) considered most likely to reflect efficacy and safety should be justified.

It should be demonstrated that the modified release formulation has the claimed release characteristics. This should ideally be demonstrated through deconvolution of the concentration-time data for the modified release formulation to an appropriate immediate release formulation (see Appendix II for more detail) to obtain the cumulative absorption (or in vivo release) versus time profile for the modified release formulation. Both the cumulative amount absorbed and rate of absorption versus time should be used to support the claimed release characteristics.

Fluctuation in drug concentrations should be studied following repeated dosing. Unless otherwise justified, the modified release product should produce similar or less fluctuations as the immediate release product.

In those cases where the modified release formulation is to be administered to patients already treated with an immediate release dosage form (switching), the time to achieve steady state concentration after switching should be addressed to define appropriate dosing instructions.

Dose levels and strengths to be evaluated

If the active substance and the MR formulation (see section 5.1.3) exhibit linear pharmacokinetic properties it may be sufficient to compare the modified release formulation and the immediate release formulation after single and multiple dose administration at one dose level.

If the active substance or the MR formulation (see section 5.1.3) exhibit non-linear pharmacokinetics (in the therapeutic plasma-concentration range) it is necessary to compare the modified release formulation and the immediate release formulation at least at the highest and the lowest dose level. If the IR and MR formulation display different extent of non-linearity additional strengths may need to be compared. This also applies if the composition of the strengths is not quantitatively proportional.

5.1.2. Variability

The inter-individual variability of the pharmacokinetic parameters of interest should be determined in the single dose or multiple dose studies described in section 5.1.1 and should be compared between the modified and immediate release formulation. The variability of the modified release formulation should preferably not exceed that of the immediate release formulation.

5.1.3. Dose proportionality

Whenever there are several strengths or when several single units can be taken simultaneously to achieve the desired dose, dose proportionality for different strengths / doses of the modified release formulations should be adequately addressed. Dose proportionality should be evaluated by means of a single dose and multiple dose study where the PK parameters of interest of all the strengths/doses are compared after dose adjustment.

5.1.4. Factors affecting the performance of a modified drug formulation

5.1.4.1. Food

The influence of food on the bioavailability of oral modified release formulations must be investigated.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high-fat high-calorie meal immediately before dosing. It is recommended that subjects should start the meal 30 minutes prior to administration of the drug product and finish this meal within 30 minutes. The meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

The design of the food effect study depends on which other studies that are conducted comparing the new oral modified release formulation with the approved immediate release formulation and if there is a clinically significant food effect on the immediate release formulation.

If there is no food effect on the immediate-release formulation, a 2-way cross-over study comparing the modified release formulation in fasted and fed states could be sufficient (given that other studies compare the modified release and the immediate release formulations under fasting conditions).

In case of a clinically significant food effect for the immediate release formulation, a 4-way cross-over study comparing the modified release formulation in fasted and fed states and the immediate release formulation in fasted and fed states could be useful to quantify the food effect on each formulation.

Whenever there are several strengths, the food effect can be investigated for one of the strengths only if the products are proportional in composition (e.g. multi-particulate dosage forms or proportional tablets), having the same manufacturing process, exhibit linear pharmacokinetics and their dissolution profiles are similar in a range of dissolution media. Generally, the highest strength should be tested, unless otherwise justified. In case the above conditions are not fulfilled, it is necessary to investigate the food effect at the highest and the lowest strengths or the extreme cases based on a bracketing approach.

For the assessment of food effect besides AUC and C_{max}, it may also be valuable to compare the modified release characteristics by verifying that the shape of the concentration – time profiles are not significantly altered.

The clinical relevance of the effect of food should be discussed both from an efficacy and a safety perspective. When needed, dose recommendations with respect to intake of the product in relation to meals should be given. Additional studies with other types of food or with intake of the product at certain time intervals before and after a meal may be needed to support the proposed dose recommendations (see also CPMP/EWP/560/95 Guideline on the investigation of drug interactions)

If the formulation or the manufacturing process is changed during drug development a new evaluation of the food effect for the final formulation may be needed.

Different type of administration: The labelling of certain multiple unit formulations can recommend that the product can be opened and the pellets/beads can e.g. be sprinkled on soft foods, dispersed in a glass of non-carbonated water and swallowed without chewing or administered through a gastric tube. For the labelling to indicate this additional type of administration, additional in vitro dissolution testing showing equivalence between the closed and the opened formulation is necessary. The absence of BE studies imitating the additional options of administration should be justified.

5.1.4.2. Gastro-intestinal function

If an oral modified release formulation is often be co-administered with active substances affecting gastrointestinal physiology (e.g. opioids) it is necessary to investigate the performance of the oral modified release formulation during these conditions.

If the oral modified release formulation is intended for patients with markedly altered gastrointestinal function the modified release formulation may need to be studied also in those patients.

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

Unintended, rapid drug release of the entire amount or a significant fraction of the active substance contained in a modified release dosage form is often referred to as “dose dumping”. Depending on the therapeutic indication and the therapeutic index of an active substance, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both.

For modified release formulations the risk for unexpected release resulting in unforeseen exposure should be excluded. If dose dumping is observed (e.g. much higher peak exposure with an inadequate modified release profile) or suspected (e.g. absence of levels of a labile active substance in gastro-resistant formulation for some subjects) the product should be reformulated to avoid this deficiency of the biopharmaceutical quality.

Much higher peak exposure might also be observed in prolonged release products due to active substance release in the stomach for an extended period of time with a subsequent absorption of the released dose once the gastric content is emptied. As this unintended increased exposure is not related to product failure, dosing recommendations should be implemented to avoid a prolonged residence in the stomach.

Effects of alcohol

Some modified-release oral dosage forms contain active substances and/or excipients that exhibit higher solubility in ethanolic solutions compared to water. Concomitant consumption of alcoholic beverages with such products may possibly induce dose dumping.

For such formulations, *in vitro* studies of the release in alcohol solutions should be performed. Where accelerated active substance release is seen in vitro either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the product should be reformulated. Only in those cases where it can be justified that an in vitro alcohol interaction cannot

be avoided by reformulation, could an in vivo study be accepted, in order to substantiate that such an interaction is unlikely to occur in vivo.

The in vivo investigation of alcohol-induced dose-dumping should compare the systemic exposure when the modified release product is ingested with a reasonable amount of alcohol on an empty stomach. The results of the study should be assessed not only with respect to the clinical relevance of the group mean change but also to the clinical consequences of the observed individual ratios.

If a significant dose-dumping effect is likely in vivo and cannot be avoided by reformulation, the benefit/risk of the product needs to be carefully considered. Contraindicating alcohol as only measure is generally not considered an appropriate means to address a formulation interaction with alcohol. Information on relevant interactions with alcohol, in case of possible clinically relevant potentiation or a harmful additive effect should be given in the product information.

In addition other label warnings and risk management strategies need to be discussed.

5.1.5. Other points to consider

5.1.5.1. Special populations

Different physiological conditions (e.g. transit times, pH, food intake) in vegetarian, paediatric and elderly patients should be taken into consideration especially when designing oral once daily MR formulations.

5.1.5.2. Influence of site of application on plasma levels (SC/IM depot formulations, TDDS)

The effect of different sites of application of SC/IM depot formulations or TDDS on the absorption of the active substance should be investigated if the application site is not limited to one body area.

Safety and tolerability at the site of application should be assessed.

In case of SC/IM depot formulations or TDDS it should be investigated that not only the plasma levels are within the therapeutic concentrations at the end of the dosing interval but also how the plasma levels decrease after removal of the depot formulation or TDDS.

5.1.5.3. Multiphasic modified release products

Rarely a modified release preparation has been developed solely in order to mimic a TID or QID dosage schedule. In these cases the modified release preparation should be equivalent with the immediate release formulation given in the dose schedule that is imitated.

5.1.5.4. Prolonged residence time in the stomach

Gastric emptying of single unit dosage forms that do not disintegrate in the stomach may be prolonged and highly erratic. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable. If for an acid labile active substance release occurs prior to stomach emptying degradation of the active substance can result and non-existing concentration profiles can be obtained.

Furthermore the release of the active substance may be considerably delayed due to a prolonged residence in the stomach. Therefore the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the active substance but also the possible occurrence of this effect to make sure that influence of delayed gastric emptying is adequately characterised.

5.2. Therapeutic studies

As a principle, comparative clinical efficacy and safety data are needed in addition to PK data for modified release products developed after the immediate release formulation, unless adequately justified. As the efficacy and safety of the immediate release product is known, the major issue would be to demonstrate that the new modified release formulation is as safe and effective as the existing formulation. Additional benefits of the new formulation should be shown or justified, if claimed.

However, in exceptional cases, if the assessment of concentration-effect relationship indicates that there is a well-defined relationship between plasma concentration(s) of the active substance /active metabolite(s) and clinical response, clinical trials may be considered unnecessary. In this case the same or a better level of efficacy and safety has to be concluded from PK/PD studies.

When assessing PK/PD relationships for modified-release products, the differential effects on efficacy and safety due to differences in rate of absorption and fluctuation should be determined since it is important not only to establish concentration - effect relationships, but also to determine the significance of differences in the shape of the steady state concentrations versus time profile for a modified release product regimen as compared to the approved immediate release product regimen. Tolerance to therapeutic effects and toxic effects related to drug exposure, concentration, absorption rate and fluctuation should also be examined as part of the PK/PD assessment. Therefore, it is essential to investigate the profile shape versus PD relationships.

5.2.1. Waiving of therapeutic studies

In principle therapeutic studies are necessary.

However, therapeutic studies might be waived when:

- bioequivalence between the immediate release and the modified release product is shown in terms of C_{max}, C_{min} and AUC at steady state because the modified product is developed to actually mimic the performance of an immediate release product and its dosage regimen e.g. a pulsatile multiphasic release dosage form containing pellets with different lag time.
- bioequivalence between the immediate release and the modified release product is shown in terms of C_{max}, C_{min} and AUC at steady state despite differences in the shape of the plasma concentration-time profile if it is possible to justify that the difference in shape has no relevance for efficacy and safety based on the exposure – response and profile shape - response relationships.
- there is a well-defined therapeutic window in terms of safety and efficacy, the rate of input is known not to influence the safety and efficacy profile or the risk for tolerance development and strict bioequivalence between the immediate release and the modified release product is shown in terms of AUC at steady state and $C_{max,ss}$ for the MR formulation is below the $C_{max,ss}$ for the IR formulation and $C_{min,ss}$ for the MR formulation is above the $C_{min,ss}$ for the IR formulation.

5.2.2. How to design clinical studies

Comparative studies should be adequately designed and conducted to assess the intensity and duration of the therapeutic effect and undesirable effects of the modified release formulation in comparison with the authorised immediate release formulation. Studies should establish the clinical benefit of the new formulation relative to the authorised immediate release formulation. 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 (e.g. assessment of breakthrough pain).

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, this may be possible if it is appropriately justified by the applicant.
- In cases when the prolonged therapeutic activity may alter the safety profile of drug during chronic dosing, safety studies may be required.

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 or equivalence. In either situation, the design and analysis of the trials should consider the recommendations of ICH E9.

Whether these pharmacodynamic/clinical studies should show equivalence or non- inferiority as compared to the standard formulation depends on the direction of the effect or safety issue at stake. In case efficacy and safety are closely related equivalence studies are needed for showing that the effect studied remains within the equivalence margins. If it is acceptable to investigate only efficacy and it is not expected that formulations have different safety, a demonstration of non-inferiority might be sufficient.

The type of studies that are required depends on whether appropriate, pharmacodynamic endpoints can be defined, whether the relationship between the pharmacodynamic markers and clinical efficacy is known, whether assay sensitivity is guaranteed and whether a non-inferiority margin or equivalence margin can be defined.

Such equivalence and non-inferiority studies may include a placebo arm beside the immediate and modified release preparation. A placebo arm or an additional active arm with a lower dose is mandatory if assay sensitivity of the trial cannot be guaranteed (see ICH E10).

In addition, equivalence margins or non-inferiority margins have to be defined and justified irrespective whether the endpoint is based on pharmacodynamic measurement or clinical variable.

If for a modified release product an indication is claimed that is different from that of the immediate release formulation a clinical development plan in accordance with existing guidelines or the state of the art is required.

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

If a claim is made for fewer systemic adverse reactions for the modified release form, this has to be substantiated.

6. Abridged application for modified release forms referring to a marketed modified release form

For orally administered products, bioequivalence studies of modified release formulations are recommended to be conducted by comparing two formulations (test versus reference) of the same pharmaceutical form. A generic MR formulation should be compared with the MR formulation that is either the originator or the line extension of an IR originator formulation, with which bioequivalence is

claimed. The general recommendations regarding study design, conduct, evaluation and reporting of bioequivalence studies detailed in the Guideline on Bioequivalence (CPMP/EWP/QWP1401/98) are applicable also for bioequivalence studies for modified release products. Aspects specific to MR formulations are detailed in this section.

If two products with the same dosage form differ in their release controlling excipients or mechanism they can be considered generics if they are bioequivalent in vivo after single dose in the fasted and fed state (see section 6.1) as well as under multiple dose conditions, if needed.

Studies are in general recommended to be conducted in healthy volunteers. However, if it is not possible to conduct studies in healthy volunteers for safety reasons, studies can be conducted in patients, preferably after both single and multiple dose administration in line with recommendations below. If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple dose studies.

In general a generic is meant to be bioequivalent with the innovator under fasted and fed conditions. A difference regarding formulation related food interactions indicates product differences thus contradicting the generic by definition. Accordingly, for products where bioequivalence can be shown in the SPC recommended condition but not in the non-recommended state due to less food effect, the product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3) application.

6.1. Prolonged release formulations for oral administration

Bioequivalence between two prolonged release formulations should be evaluated on the basis of studies designed to demonstrate that:

- the test formulation exhibits the claimed prolonged release characteristics of the reference;
- the active substance is not released unexpectedly from the test formulation (no 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.

The following studies are generally required to demonstrate bioequivalence:

- a single-dose fasting study comparing test and reference drug product
- a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference drug product
- a multiple-dose study comparing test and reference drug product.

Single dose studies

One of the following schemes is recommended for single dose evaluation in fasting and fed state:

- A four-period cross-over trial with four complementary sequences of four treatment conditions. Both the test and reference products should be assessed in the fasting state as well as after the administration of a high fat meal at a specified time before taking the drug.
- Two cross-over trials. The first trial should compare the test and reference products under fasting conditions. The study treatments should be administered during two periods and with two sequences of treatment conditions. The second trial should compare the test and reference

formulations following the administration of a high-fat meal at a specified time before taking the study treatment, as well as the test formulation under fasting conditions. The trial should be conducted with three periods and three complementary sequences of drug administrations.

- Two cross-over trials, both with two periods and two sequences of test and reference product administration. One trial should be conducted in the fasting state. The other trial should be conducted after the administration of a high fat meal at a specified time before taking the study treatment.

Multiple dose studies

A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected. In this case bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in the single dose study (see also section 6.8.2). An early $_{partial}$AUC and a terminal $_{partial}$AUC separated by a predefined time point, which is usually the half of the dosage interval are recommended, unless otherwise scientifically justified.

In all other cases, where accumulation is likely ($AUC_{(0-\tau)}$ after the first dose covers less than 90% of mean $AUC_{(0-\infty)}$) a multiple dose study is required. Generally, steady-state studies should be performed under the conditions concerning concomitant food intake recommended in the SmPC for the originator product. If the SmPC states that the product has to be taken in fed condition only the study should be performed in fed conditions, although it only needs to be high fat high calorie content on the day of profiling. If the SmPC states that the product should be taken in fasted state or irrespective of food intake the studies should be performed in fasted conditions.

In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment (direct switching), provided the build-up period is sufficiently long (at least 5 times the terminal half-life).

Whether the steady-state has been achieved is assessed by comparing at least three pre-dose concentrations for each formulation. The apparent half-life should also be taken into account.

Note:

The discussion of the opportunity of using equivalence in C_τ in single dose studies as basis for waiving the multiple dose study has been recognized. However, there is not considered to be sufficient scientific evidence at the moment to encourage this approach.

6.1.1. Strength(s) to be evaluated

Single unit formulations

For single unit formulations with multiple strengths the following considerations apply:

A. Single dose studies

- If the reference SmPC recommends intake in the fasting state or irrespective of food intake,
  - Fasting state: a single dose study under fasting conditions is required for each strength. However a bracketing approach (see section 6.6) is also possible if justified.
  - Fed state: One single dose bioequivalence study at the highest strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if

the strengths of the test product do not fulfil these criteria or if proportional strengths have different size/shape two strengths representing the most extreme difference should be tested in fed state.

- If the reference SmPC recommends intake under fed conditions,
  - Fed state: a single dose study under fed conditions is required for each strength. However, a bracketing approach (see section 6.6) is also possible if justified.
  - Fasting state: One single dose bioequivalence study at the highest strength conducted in fasting state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if proportional strengths have different size/shape two strengths representing the most extreme difference should be tested in fasting state.

B. Multiple dose studies

- A multiple dose study should be performed with the highest strength (unless it is shown that there is no accumulation as detailed in section 6.1). The other strength(s) can be waived if the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled.

Multiple unit formulations

For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1 only at one strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturer) and the dissolution profiles are similar fulfilling the criteria of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98). If the pharmacokinetic of the originator modified release product are linear the studies can be conducted at any strength. If the pharmacokinetic of the originator modified release product are non-linear the studies must be conducted with the most sensitive strength as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

6.2. Delayed release formulations

The following studies are generally required to demonstrate bioequivalence:

- a single-dose fasting study comparing test and reference product
- a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference product

6.2.1. Strength(s) to be evaluated

A similar approach as detailed for prolonged release forms regarding study design of single dose studies can be used (see 6.1).

Single unit formulations:

- If the reference SmPC recommends intake under fasting state or irrespective of food intake,
  - Fasting state: a single dose study under fasting conditions is required for each strength. However a bracketing approach (see section 6.6) is also possible if justified.
  - Fed state: One single dose bioequivalence study at the highest strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the

investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if proportional strengths have different size/shape two strengths representing the most extreme difference should be tested in fed state.

- If the reference SmPC recommends intake under fed conditions only,
  - Fed state: a single dose study under fed conditions is required for each strength. However a bracketing approach (see section 6.6) is also possible if justified
  - Fasting state: One single dose bioequivalence study at the highest strength conducted in fasting state may be sufficient. The other strength(s) can be waived if the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if proportional strengths have different size/shape two strength representing the most extreme difference should be tested in fasting state.

When evaluating proportionality in composition, the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) should be considered to have the same gastro-resistance (coating layer in mg/cm^2 surface).

Multiple unit formulations:

For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed under 6.2 at one strength only, if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturer) and the dissolution profiles are similar. If the pharmacokinetics of the originator delayed release product is linear the studies should be conducted at the highest strength unless otherwise justified. If the pharmacokinetic of the originator modified release product are non-linear the studies must be conducted with the most sensitive strength as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

6.2.2. Prolonged residence time in the stomach

Gastric emptying of single unit dosage forms that do not disintegrate in the stomach (e.g. enteric coated tablets) may be prolonged and highly erratic. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable. If the active substance release occurs prior to stomach emptying degradation of the active substance can result and non-existing concentration profiles can be obtained. If the incidence of this outlier behaviour is observed with a comparable frequency in both, test and reference product, data of a period with non-existing profile can be excluded from statistical analysis provided that it has been pre-specified in the study protocol. In a 2-period trial this will result in the subject being removed from the analysis.

Furthermore the release of the active substance may be considerably delayed due to a prolonged residence in the stomach. Therefore the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the active substance but the possible occurrence of this effect as well.

6.3. Multiphasic modified release products

The regulatory criteria mentioned in this Guideline are also applicable in the assessment of bioequivalence for modified release products designed to achieve sequential release combining immediate and modified characteristics (e.g. biphasic-/ pulsatile-release).

If one of the release phases is prolonged, the type of studies required are those described in section 6.1.

However additional pharmacokinetic parameters are needed to demonstrate bioequivalence for all phases (see section 6.8.1).

6.4. Intramuscular/Subcutaneous Depot Formulations

The following studies are generally required:

- a single-dose study comparing test and reference products
- a multiple-dose study comparing test and reference products.

A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that:

- the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected

6.4.1. Strength to be evaluated

Only one strength has to be investigated if the different strengths are proportional in composition and exhibit a similar in vitro dissolution profile. The strength should be selected based on the pharmacokinetic linearity and safety. If there are several non-proportional strengths a bracketing approach is possible.

If the originator product is marketed in only one concentration and the different doses are achieved by choosing the total volume to be injected any dose should be acceptable for a bioequivalence trial in case dose proportionality can be shown.

6.5. Transdermal Drug Delivery Systems (TDDS)

A generic TDDS is defined by having the same amount of active substance released per unit time as compared to the reference TDDS. It is to note that this definition is different to the general definition of a generic since the overall amount of active substance could differ while the labelled amount of active substance released per unit time should be the same between a generic and the innovator TDDS.

Equivalence testing of TDDS should comprise both non-inferiority in terms of adhesion and bioequivalence. It is advisable to ensure adhesion equivalence prior to bioequivalence investigations in volunteers since inferior adhesion could invalidate the pharmacokinetic results and question the acceptability of the product. Bioequivalence of TDDS should generally be assessed after single dose as well as after multiple dose application. The study design including the site of application should be justified in terms of its sensitivity to detect formulation differences. The application site should be highly standardized and be the same for both test and reference.

Bioequivalence should be assessed using the same main characteristics and statistical procedures as for prolonged release formulations including fluctuation. In addition, evaluation of lag-times and profile shape is recommended.

6.5.1. Strength to be evaluated

When the marketing authorisation of multiple strengths is required, bioequivalence study can be performed with the highest strength provided that:

- the qualitative composition is the same for all strengths;
- the strengths are proportional to the effective surface area of the patch and the lower dose strengths can be considered as ''partial'' areas of the highest dose strength;
- there are similar dissolution/release profiles

In case of safety / tolerability limitations at the highest strength, the use of a lower strength is acceptable for size proportional formulations.

The test product should demonstrate a similar or less degree of local irritation, phototoxicity, sensitization, and similar or better adhesiveness to the skin as the reference product. In order to ensure equivalence in terms of safety, comparative state-of-the-art studies are required to investigate

- cutaneous tolerability, irritation and sensitisation (see appendix 1)
- the potential to produce phototoxic reactions
- adhesion characteristics

unless otherwise justified by e.g. very similar quantitative and qualitative composition.

For details regarding comparative adhesion tests reference is made to Guideline on quality of transdermal patches (EMA/CHMP/QWP/911254/2011).

6.6. Bracketing approach

Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition or for single unit formulations with proportional composition, a bracketing approach may be used in special cases, where the other waiver criteria (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition or dissolution, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies.

However, for prolonged release formulations release-controlling excipients and mechanism should be the same for all strengths. The same is required for release controlling coatings for delayed release formulations.

6.7. New strength for an already approved MR product

Section 6 also applies to the development of a new strength within the existing dose range. For a new strength with proportional composition to approved strength(s) a bracketing approach may be applicable. For a new strength with non-proportional composition to approved strength(s), the new strength has to meet the requirements as described in relevant sections above (section 6.1-6.5).

A new strength outside the existing range requires a clinical development.

6.8. Evaluation

6.8.1. Parameters to be analysed

Single dose studies:

In studies to determine bioequivalence after a single dose, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max}, $_{partial}AUC$ and t_{max} should be determined. A truncated $AUC_{(0-72h)}$ is not acceptable for MR products.

For multiphasic modified release products additional parameters to be determined include $_{partial}AUC$, C_{max} and t_{max} in all phases. The time point for truncating the $_{partial}AUC$ should be based on the PK profile for the IR and the MR parts respectively and should be justified and pre-specified in the study protocol.

Steady state studies:

In studies to determine bioequivalence after a multiple dose administration $AUC_{(0-\tau)}$, $t_{max,ss}$, C_{maxss}, $C_{\tau ss,}$ and fluctuation should be determined. In contrast to the need of characterisation of $C_{min,ss}$ for new MR formulations, a comparison of $C_{\tau,ss,}$ which is easier to determine, should be sufficient.

6.8.2. Acceptance criteria

Bioequivalence should be demonstrated by showing equivalence after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, $_{partial}AUC$

Multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$

For prolonged release products with no risk of accumulation (see section 6.1) a statistical evaluation of the following parameters has to show bioequivalence:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and a representative parameter of the shape of the curve (early and terminal $_{partial}AUC$s)

The bioequivalence approach considering usual acceptance limits (80 – 125 %) is applicable for generic MR products (see CPMP/EWP/QWP/1401/98). Any widening of the acceptance criteria for C_{max} should follow the recommendations on highly variable drug products in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

A similar approach can be used for widening the acceptance criteria for $C_{max,ss}$, $C_{\tau,ss}$, and $_{partial}AUC$.

For delayed and multiphasic release formulations differences in t_{max} is also recommended to be assessed, especially for products where a fast onset of action is important. A formal statistical evaluation of t_{max} is not required. However, there should be no apparent difference in median t_{max} and its range between test and reference product.

6.9. Effects of alcohol

For generic oral formulations, *in vitro* studies of the release in alcohol solutions should be performed. Where accelerated active substance release is seen in vitro either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the product should be reformulated.

If the alcohol effect cannot be avoided and it is present also in the reference product, the applicant should justify / demonstrate that it lacks of clinical relevance.

6.10. Further points to consider for bioequivalence studies

The following issues should be handled in line with the recommendations for immediate release formulations stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)

- Test and reference product
- Subjects
- Study conduct
- Statistical evaluation of primary endpoints
- Parent compound or metabolites
- Enantiomers
- Endogenous substances
- Narrow therapeutic index drugs (in addition narrowing of the acceptance criteria of C_τ might be necessary)
- Highly variable drugs or drug products
- Linearity

Definitions

$AUC_{(0-t)}$:	Area under the plasma concentration curve from administration to last observed concentration at time t;
$AUC_{(0-\infty)}$:	Area under the plasma concentration curve extrapolated to infinite time;
$AUC_{(0-72h)}$	Area under the plasma concentration curve from administration to 72h;
$_{partial}AUC$:	partial AUC
C_{max}:	Maximum plasma concentration;
residual area	Extrapolated area ($AUC_{(0-\infty)}$ - $AUC_{(0-t)}$)/ $AUC_{(0-\infty)}$;
t_{max}:	Time until C_{max} is reached;
t1/2:	Plasma concentration half-life;
λ_z:	Terminal rate constant;
$AUC_{(0-\tau)}$:	AUC during a dosage interval at steady state
$t_{max,ss}$:	Time until $C_{max,ss}$ is reached
$C_{max,ss}$:	Maximum plasma concentration at steady state
$C_{min,ss}$:	Minimum plasma concentration at steady state
C_{τ}:	Concentration at the end of the dosing interval
$C_{\tau,ss}$:	Concentration at the end of the dosing interval at steady state
C_{av}	average concentration during a dosing interval ($AUC_{(0-\tau)}$ / τ)
fluctuation	[(C_{max}-C_{min})/C_{av}]
t_{lag}	lag time

Appendix I (sensitisation and irritation test for transdermal products)

This appendix is intended to recommend study designs and scoring systems that can be used to test skin irritation and sensitization during development of transdermal products.

The condition of the skin may influence the absorption of an active substance from a transdermal system and affect the efficacy or safety of the product. Therefore skin irritation and sensitization should be assessed.

To fully evaluate the equivalence of a generic transdermal product to the reference product similarity has also to be shown for skin irritation and sensitization unless otherwise justified by e.g. very similar quantitative and qualitative composition.

The strength chosen for the test is determined by considering the following factors:

- previous human experience
- previous sensitisation/irritation tests in animals

Overall Study Design for a generic application

The study suggested has an active- and placebo-controlled, multiple-dose, three-phase, parallel-group design.

Screening evaluations are performed within a 14-day period prior to application of the patches.

Screening evaluations should consist of a medical history, complete physical examination, 12-lead electrocardiogram (ECG), laboratory evaluations (including serum chemistry, hematology, and urinalysis), and urine drug screen.

Subjects are assigned to one of two analysis groups (Group 1 and Group 2) and are evaluated for both cumulative dermal irritation and contact sensitization. Test, reference and placebo transdermal patches should be applied to randomly assigned test areas on the backs of subjects in the two groups. Application areas are upper left back, upper right back, or left back below according to a randomization scheme within each subject. Skin reactions have to be evaluated by a trained observer blinded to the treatment.

Criteria for discontinuation of the test should be mentioned in order to avoid excessive reaction.

Each subject participates in the following three consecutive study phases.

Induction/Cumulative Irritation Phase

Group 1 subjects apply test, reference, and placebo patches to randomly assigned treatment areas for 21 consecutive days.

Group 2 subjects apply test, reference, and placebo patches to randomly assigned treatment areas three times weekly over a period of 21 days (a total of nine applications). In Group 2, the patches remain in place for 48 hours (on weekdays) and 72 hours (on weekends). The new patch should be applied to the same site as the previous patch.

Rest Phase

Following the Induction/Cumulative Irritation Phase, each subject enters a 2-week Rest Phase. No patches are applied during the Rest Phase.

Challenge Phase

Following the Rest Phase, patches are applied to new skin sites within the designated areas for 48 hours.

In addition to dermal assessments at 0.5 and 24 hours after patch removal, subjects participating in the Challenge Phase also return for examination on Days 40 and 41 for additional dermal assessments at 48 and 72 hours after removal of the last patch.

To minimize the effect of inter-subject variability, each study participant receives all three treatments simultaneously. In addition, to control for the unlikely possibility of a treatment-by-site-interaction, the three treatments should be randomly assigned to three application areas so that each treatment occupied each application area with approximately equal frequency throughout the panel of study participants.

Group 1	**Cumulative Irritation Phase**				
	Test, Reference Placebo	One patch of each drug applied daily to the back of each subject for 21 days			
	Induction of Contact Sensitization		**Rest Phase**	**Challenge Phase**	
	Test, Reference Placebo	One patch of each drug applied daily to the back of each subject for 21 days	No patches applied tor 2 weeks	Test, Reference Placebo	One patch of each drug applied to the back of each subject; patch removed after 48 hours
Group 2	**Induction of Contact Sensitization**		**Rest Phase**	**Challenge Phase**	
	Test, Reference Placebo	One patch of each drug applied to the back of each subject three times a week over a period of 21 days	No patches applied tor 2 weeks	Test, Reference Placebo	One patch of each drug applied to the back of each subject; patch removed after 48 hours

Dermal response has to be assessed for all subjects in Group 1 and Group 2. Application sites for both groups are evaluated for skin irritation 30 minutes after patch removal (dermal response and other effects scores determined), and new patches are applied 1 hour after removal every time that the patch is removed during the Induction/Cumulative Irritation Phase.

To evaluate contact sensitization during the Challenge Phase, test, reference, and placebo patches are applied simultaneously for 48 hours to previously unused sites on Group 1 and Group 2 subjects. Application sites were evaluated at 0.5, 24, 48, and 72 hours after patch removal.

Skin reactions can be examined and graded using the numerical and letter scores outlined in Table 1 (dermal response) and Table 2 (other effects).

Each application site receives a separate dermal response score and other effects score. Dermal response scores require that at least 25% or more of the patch area demonstrate an observable response. During the Challenge Phase (contact sensitization evaluation), only combined dermal response scores ≥2 are considered a positive response.

Table 1	**Dermal Response Score**
Score	**Definition**
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Table 2	**Dermal Response Score**
Score	**Definition**
0	None observed
1	Slight glazed appearance
2	Marked glazing
3	Glazing with peeling and cracking
4	Glazing with fissures Film of dried serous exudates covering all or part of the patch site Small petechial erosions and/or scabs

"Strong" reaction to the test patch are defined as a dermal response score of 3-7 or any dermal score combined with another effects rating of 4.

Group	**Phase**	**Evaluation by observer**	**Assessment of Test, Reference and Placebo**
Group 1	Cumulative Irritation Phase	Dermal Response Score Other Effects Score	• Mean Irritation Score = average of Dermal Response Scores • Total Cumulative Irritation Score sum of Dermal Response Scores • Combined Dermal Response Score sum of Dermal Response Score and Other Effects Score • Mean Combined Dermal Response Score
Group 1 + 2	Challenge Phase (Contact Sensitization)	Dermal Response Score Other Effects Score	-Combined Dermal Response Score 2:2

The primary analysis compares the test and reference treatments for the mean irritation scores (average numeric dermal response over the observations) and the total cumulative irritation scores (sum of the numeric dermal response scores over the observations). The two one-sided t-test method should be used to compare the irritation scores between treatments. For each parameter, least squares means for each treatment are derived from an ANOVA model where subject and treatment are fixed effects. The ratio of the least squares means of the test treatment to the reference treatment has to be calculated, along with its 90% confidence interval. A 90% confidence interval that falls completely within the interval 0.8 to 1.25 leads to the conclusion that the two treatments are equivalent.

931 The assessment of contact sensitization consists of tabulations of dermal response scores ≥2 during
932 the Challenge Phase. No statistical analysis has to be performed on these data.

933

Appendix II (In vitro in vivo correlation):

1 Introduction

An *in vitro in vivo correlation* (IVIVC) is a mathematical model describing the relationship between an *in vitro* property of a dosage form (mainly dissolution or drug release) and a relevant *in vivo* response (mainly drug plasma concentration or amount absorbed).

When a modified release formulation is developed, it is highly recommended to establish an IVIVC:

a) to quantify in vivo release and formulation related effect on absorption,

b) to establish the clinical relevance of in vitro dissolution tests and associated dissolution specifications

c) to support biowaiver claims in later phases of clinical development or post-authorisation if there are changes in formulation.

Historically different levels of IVIVC relationships have been described; including levels A, B and C (see Annex 2, Guideline on quality of oral modified release products EMA/CHMP/QWP/467527/2012). Level A IVIVCs, in contrast to levels B and C, predict the entire concentration-time profile and for this reason are highly encouraged. Where an IVIVC is used to support regulatory decisions such as dissolution specification or biowaiver, a validated level A correlation is a prerequisite.

The usefulness of an IVIVC depends on how accurately it can predict resultant plasma concentrations from any given set of in vitro data. This in turn is heavily dependent on the design of the in vitro and in vivo studies used to develop and validate the IVIVC.

2 Study Design Considerations

Generally, two or more formulations with sufficiently different dissolution profiles and an appropriate reference formulation (for the purpose of deconvolution) with fast drug release (e.g., oral solution or immediate release formulation) are administered in a crossover study in healthy volunteers. For modified release products, the IVIVC study is normally conducted in the fasted state, even when the product is recommended to be taken with food. Parent drug levels are quantified as a function of time in blood or plasma.

Extrapolation beyond the range of formulations used in IVIVC development and validation is not acceptable for regulatory applications (e.g. specification setting and biowaiver requests). Thus, the choice of formulations requires careful consideration. This is further discussed in the Guideline on quality of oral modified release products (EMA/CHMP/QWP/467527/2012). As the sensitivity of the plasma concentration-time profile for a given drug will depend on its particular disposition properties, it is advisable to base IVIVC formulation selection on expected plasma concentration-time profiles (simulated using an assumed IVIVC relationship or range of possible relationships and the known disposition characteristics of the drug).

While it is acceptable to use different dosage strengths to establish an IVIVC or for external validation, it should be noted that different dosage strengths of the same formulation would generally not be considered to represent “different” release rates. For this reason, judgement of whether the dissolution profiles for different formulations are “different” is normally based on % of labelled (or actual) content.

2.1 Role and Choice of Reference Formulation

A reference formulation is a fast-releasing formulation included in IVIVC studies to allow calculation of the in vivo release of drug as a function of time for each MR formulation (see section 3.2). The in vivo

release-time profile is normally obtained by deconvolution and truly reflects drug release in vivo only when the reference formulation is an oral solution (and there is no precipitation from this solution in the stomach or GI tract). Immediate release formulations can be used as reference products in IVIVC studies and will also allow adequate approximation of the in vivo drug release from the MR formulations as long as the rate of dissolution from the IR formulation is fast relative to its absorption (which is normally the case for the drugs that are chosen as suitable for MR product development). Sometimes IV product is used as the reference for IVIVC. This will also allow adequate approximation of in vivo drug release as long as absorption is fast (i.e. for drugs with high permeability).

A reference formulation should be included in any study where the data will be used to support the development and internal or external validation of the IVIVC.

2.2 Sampling Times

Considerations for the choice of in vitro sampling times are discussed in the Guideline on quality of oral modified release products (EMA/CHMP/QWP/467527/2012). Although discussed separately, an integrated approach to the design of the IVIVC study (including in vitro dissolution and in vivo blood/plasma sampling times) is encouraged.

Sampling time decisions for blood/plasma are best made based on simulations using the actual (or modelled) in vitro release data for the clinical batches manufactured for the IVIVC study. If the in vitro dissolution is pH or rotation-speed dependent, it is useful to do simulations using the range of in vitro dissolution profiles in order to design a sampling regimen to cover the range of potential in vivo behaviours. Also, if there is some *a priori* understanding of the likely IVIVC relationship this is best built into the initial simulation. For example, for injectable controlled release formulations, in vitro release testing is often designed to be complete within 24-48 h, while the in vivo delivery is designed to continue for 1-2 months. Thus, a time-scaling factor (or range of factors) can be anticipated *a priori* and built into the model to provide a more realistic picture of the expected in vivo behaviour and better choose appropriate sampling times for the test formulations.

2.3 Number of Subjects

The number of subjects to be included in an IVIVC study is dependent, as for the design of BE studies, on the variability of the drug product. Although no firm guidance can be given, a pragmatic approach would be to use no fewer than 12 in a crossover IVIVC study.

3 IVIVC Development and Validation

3.1 General Considerations

The overall goal of IVIVC is to be able to reliably predict the entire time course of plasma concentration from a modified release formulation based on in vitro release data. In principle any methodology that is scientifically sound can be used for this. Although a few are discussed below, methodology will continue to evolve and this list should not be considered to be exhaustive. As the purpose of the IVIVC is to be able to predict without in vivo testing the plasma concentration resulting from a modified formulation with different in vitro release data, it is a prerequisite that a single IVIVC relationship is applicable to all formulations used in its development and validation.

3.2 Acceptable Methods of Data Analysis

Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is deconvolution-based. One stage approaches include convolution-based and differential equation-based methods.

Deconvolution-based methods involve two stages of data analysis. The first stage employs deconvolution to estimate the time course of in vivo absorption. Noncompartmental methods of deconvolution are preferred. The second stage establishes the relationship between cumulative in vivo absorption and in vitro drug release. A linear relationship between in vivo absorption and in vitro release, although desirable, is not necessary and there are many physiological and physicochemical factors that make this less likely. In principle, any relationship that is applicable to all IVIVC formulations is acceptable including sigmoidal, Hill, incorporation of time-scaling and time-shifting parameters and approaches to account for incomplete absorption (absorption cut-off time, nonlinear absorption functions) with justification based on an understanding of the formulation, physicochemical, pharmacokinetic and physiological factors controlling drug release in vitro and vivo. Different time scales for each formulation points to the absence of a single relationship for the IVIVC formulations. Deconvolution-based methods are particularly helpful for exploratory data analysis during the model building process, as they provide graphical output (cumulative amount absorbed in vivo versus cumulative amount released in vitro and Levy plots: time for a specific %of dose absorbed in vivo versus time for a specific % of dose released in vitro) that can be used to identify appropriate models for the IVIVC relationship and provide appropriate initial parameter estimates necessary for one-stage modelling methods.

Convolution-based and differential equation-based methods are classified as single stage because modelling involves utilising the observed data directly without transformation (i.e. through deconvolution). Single stage approaches offer a number of advantages over deconvolution based methods, as the model predicts directly the plasma concentration-time course; modelling focuses on the ability to predict measured quantities, not indirectly calculated quantities such as the cumulative amount absorbed; and the results are more readily interpreted in terms of the effect of the in vitro release on conventional bioequivalence metrics. Additionally, the compartmental approach allows for non-linear (e.g. Michaelis-Menten) disposition kinetics, whereas the convolution-based method assumes linear disposition. Although both convolution-based and differential-based methods are single stage, they differ in the form of the relationship between in vitro release and plasma drug concentration. The convolution-based approach uses an integral transform, such as:

$$C(t) = r(t) * C_{\delta} = \int_0^t C_{\delta}(t-\tau) r(\tau) d\tau$$

where C is plasma concentration, r is the in vivo input rate, C_{δ} is the unit impulse response (i.e. the plasma concentration profile resulting from instantaneous absorption of a unit dose of drug) and * is the convolution operator.

The differential equation-based approach utilises a traditional compartmental model framework for drug disposition and incorporates an input function.

In both cases, an IVIVC equation quantifies the relationship between drug release in vitro [$r_{dis}(t)$] and drug absorption in vivo [r(t)]. The simplest relationship is where drug dissolution reflects its rate of drug absorption. In this case:

$$r(t) = r_{dis}(t)$$

Various more complex functions that account for time lags for absorption, different time scales for in vitro dissolution and in vivo absorption and changing permeability through the gastrointestinal tract can be incorporated into the IVIVC equation. For example, the following equation includes a lag time (t_0), a time scaling factor (s_1), a time-dependent multiplying factor [$\varphi_{abs}(t)$] that accounts for changing permeability and a scaling factor (s_r) that allows incomplete absorption or utilisation of different units between in vitro dissolution and in vivo absorption.

$$r(t) = \varphi_{abs}(t) s_r r_{dis}(t_0 + s_1 t)$$

Most IVIVC analyses use averaged in vitro dissolution to predict an averaged in vivo concentration-time profile. This approach does not address adequately random variation in vitro, but more importantly, in vivo. From this point of view the one stage approaches offer the advantage that they are amenable to a nonlinear mixed effects analysis framework, which allows individual variability to be incorporated into the model, potentially improving the reliability of the model for inferences regarding the bioequivalence metrics of new formulations.

Where a two-stage approach is utilised, the average absorption profile should be derived from averaging of the individual subject absorption profiles (i.e. from individual deconvolution), rather than by deconvolution of the average concentration-time profiles.

3.3 IVIVC Model Qualification and Predictability Assessment

Model selection should be based on an understanding of the physicochemical properties of the drug, its absorption characteristics, the dissolution test characteristics and criteria for assessing goodness of fit (e.g. posterior predictive check). General requirements for model evaluation within the nonlinear mixed effects context are outlined in detail in the Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06). The purpose of the model is to be able to predict with adequate accuracy the expected plasma concentration-time curve from an in vitro dissolution data for a modified formulation. This is demonstrated by a graphical comparison of predicted and observed concentrations and calculation of prediction errors for summary parameters including at least C_{max}, AUC_{0-t} and $_{partial}AUC$ (see section 6.8.1).

An IVIVC model is generally accepted as adequately accurate if from visual inspection the entire concentration-time curve is well predicted and the prediction errors are within acceptable limits. Internal predictability is assessed using the IVIVC model to predict the concentration-time profile from the respective dissolution data for each formulation. The summary parameters (C_{max}, etc.) are calculated from the predicted concentration-time curve and compared to the respective summary parameters for the observed data. The prediction error (PE), defined as %PE =[(observed value - predicted value) /observed value] x 100, is calculated for each of the summary parameters. The absolute value of the prediction error for all summary parameters should be less than 15% for each formulation and on average for all formulations included in IVIVC development should be less than 10% for each summary parameter. Where an individual formulation is found to be inadequately predicted by the IVIVC, it is acceptable to redevelop the IVIVC excluding the outlier formulation, resulting in a narrower range of dissolution data included in the IVIVC. However, this will then determine the range over which the IVIVC is accepted as predictive, impacting on the potential for specification and biowaiver justification.

In addition to evaluation of internal predictability utilising the batches included in a formal IVIVC study, it is encouraged to continue to demonstrate the applicability of the IVIVC with additional development batches (e.g. large scale batches used in pivotal studies, additional dosage strengths, any later formulation changes that were studied in vivo, etc.). The procedure for external predictability analysis is as described above utilising the IVIVC previously developed. The concentration-time profiles are predicted based on the reference immediate release product pharmacokinetics observed in the study used for external validation purposes and the in vitro dissolution data for the particular external validation batch. The absolute value of the prediction error for all summary parameters should be less than 10% for each formulation used for external validation.

3.4 Reporting

The IVIVC report should include a listing of all in vivo studies available for the modified release formulation and a rationale for the selection of data included in IVIVC analysis. Data listings should include: individual data and summary statistics for in vitro dissolution data, plasma concentration-time data, derived pharmacokinetic parameters and cumulative amount absorbed (derived from deconvolution, even if a one stage method is used for model development) for all batches used in model development.

Graphical displays should include in vitro dissolution versus time (highlighting batches of clinical significance, such as the to-be-marketed formulation, etc.), cumulative amount absorbed versus time, absorption rate versus time, overlay of dissolution and absorption time courses (to judge different time frames, time lags between in vitro and in vivo data) and cumulative amount absorbed in vivo versus amount released at same time in vitro (with overlay of 1:1, regression lines as helpful/appropriate) for all formulations included in IVIVC analysis. A Levy plot (time for a specific fraction released in vivo versus the time for the same fraction in vitro) may also be a useful graphical display where an obvious time difference exists between time courses of in vitro release and in vivo absorption.

The dissolution test method should be described and a justification of its appropriateness given the physicochemical properties of the drug, etc. should be included.

A full description of the modelling methodology and software employed and basis of decisions should be included, supported by a discussion of the formulation, physicochemical, pharmacokinetic and physiological factors controlling drug release in vitro and vivo. Where a compartmental deconvolution method is used (e.g. Wagner-Nelson or Lou-Riegelman), the appropriateness of the approach should be discussed.

Plots evaluating goodness of fit, appropriate to the modelling methodology employed, should be included as well as final parameter estimates for all fitted data (e.g. in vitro dissolution and in vivo absorption in case a model is used for interpolation, as well for the IVIVC model itself).

The final IVIVC model predicted plasma concentration-time data, derived parameters and associated prediction error should be included in a table. Graphical comparison of predicted and observed concentration-time profiles should be provided.

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Appendix III: Summary of study recommendations for abridged applications:

Prolonged release single unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study**	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	yes	waiver	waiver
low	yes	waiver	waiver

* see criteria for necessity in section 6.1

** bracketing approach possible if criteria (see section 6.6) are met

Prolonged release single unit formulation (SmPC recommends intake under fed conditions)

Strength	Single dose fasting study	Single dose fed Study**	Multiple dose study*
high	yes	yes	yes
middle	waiver	yes	waiver
low	waiver	yes	waiver

* see criteria for necessity in section 6.1

** bracketing approach possible if criteria (see section 6.6) are met

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

Prolonged release multiple unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

* see criteria for necessity in section 6.1

Prolonged release multiple unit formulation (SmPC recommends intake fed conditions)

Strength	Single dose fasting study	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

* see criteria for necessity in section 6.1

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

Delayed release single unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study**	Single dose fed Study
high	yes	yes
middle	yes	waiver
low	Yes	waiver

** bracketing approach possible if criteria (see section 6.6) are met

Delayed release single unit formulation (SmPC recommends intake under fed conditions)

Strength	Single dose fasting study	Single dose fed Study**
high	Yes	yes
middle	waiver	yes
low	waiver	yes

** bracketing approach possible if criteria (see section 6.6) are met

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

Delayed release multiple unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

Delayed release multiple unit formulation (SmPC recommends intake under fed conditions)

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible