EMA/EGA Joint Workshop on the Impact of the Revised EMA Guideline on Modified Release Dosage Forms

Line extension of immediate release products

London, 30th April 2014

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5. Application for a MR formulation of a drug that is authorised as IR f.

- **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)**

5. Application for a MR formulation of a drug that is authorised as IR f.

- **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, unless otherwise justified as mentioned in section 5.2**.

5. Application for a MR formulation of a drug that is authorised as IR f.

- The **new formulation** should be **characterised** in appropriate **single dose and multiple dose pharmacokinetic, pharmacodynamic and clinical efficacy/safety studies**
- **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

5. Application for a MR formulation of a drug that is authorised as IR f.

- **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.

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**)

no intra-

5.1 Pharmacokinetic studies

- 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
- **Active metabolites should be measured** since a **change in absorption rate or route** of administration **may modify** the **extent and pattern of metabolism**

5.1 Pharmacokinetic studies

- In terms of **concomitant food intake**, the **multiple dose BA study** should be performed **under the SmPC** labelled **condition** during dosing to steady state.
- **If the SmPC states a certain timing of food intake in relation to drug administration**, **this timing should be used** throughout the study, **also on the day of PK profiling**

5.1 Pharmacokinetic studies

- **If the SmPC recommends intake in the fasted state (without specifying time frame) or irrespective of food**, a worst-case fasted condition (e.g. **overnight fast before** and continued 4 h after dose) should be in general be used **on the day of profiling**.
- **If the SmPC recommends intake under fed conditions normo-caloric meals** should be used **throughout the study including profiling days** unless different meal conditions are requested by the SmPC.

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
- **if there is accumulation** also following **repeated dosing**

5.1.1 Rate and extent of absorption, fluctuation

- The **pharmacokinetic parameters** of interest may be for **single dose studies**
  - $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, residual area,
  - C_{max}, t_{max}, $t_{1/2}$ and t_{lag} and
- for **multiple dose studies**
  - $AUC_{(0\text{-}\tau)}$,
  - $t_{max,ss}$, $C_{max,ss}$,
  - $C_{min,ss}$ and fluctuation

5.1.1 Rate and extent of absorption, 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**

5.1.1 Rate and extent of absorption, fluctuation

- It should be **demonstrate**d that the modified release formulation has the **claimed release characteristics**

5.1.1 Rate and extent of absorption, fluctuation

- **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.

Justified with clinical data, since clinical data is needed generally

5.1.1 Rate and extent of absorption, fluctuation

- 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, in case of drug accumulation, after multiple dose** administration **at one dose level** (see also recommendations given in section 6, General considerations)

Dose levels and strengths to be evaluated

- **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**

Dose levels and strengths to be evaluated

- **If the IR and MR formulation display different extent of non-linearity additional strengths** may need to be **compared**

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 unless it is adequately justified in terms of potential clinical consequences

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, in case of drug accumulation, multiple dose study** where the **PK parameters** of interest of all the strengths/doses are **compared after dose adjustment**

5.1.3. **Dose proportionality**

- The **criteria** described in the Guideline on the Investigation of **Bioequivalence** (CPMP/EWP/QWP/1401/98) for dose proportionality based **on AUC only and 25% acceptance range are not applicable** in this case since this criteria only apply for strength selection for BE studies

5.1.4. **Factors affecting** the performance of a MR formulation

5.1.4.1. **Food**

5.1.4.2. **Gastro-intestinal function**

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

5.1.4.1. Food

- The **influence of food on the bioavailability** of oral modified release formulations must be **investigated in a single dose study**
- 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 min**

5.1.4.1. Food

- 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** (%)).

5.1.4.1. Food

- **If there is no clinically relevant 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)

5.1.4.1. Food

- In case of known **clinically significant food effects 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

5.1.4.1. Food

- 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), have 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**

5.1.4.1. Food

- 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 Cmax**, it may also be valuable to compare the modified release characteristics by v**erifying that the shape of** the concentration – time **profiles are not significantly altered**

e.g. by means of partial AUC

5.1.4.1. Food

- 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

5.1.4.1. Food

- **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)

5.1.4.1. Food

- 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**

5.1.4.1. Food

- For the labelling to indicate this additional type of administration, **additional stability and 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 to be usually **co-administered** with active **substances affecting gastrointestinal physiology** (e.g. opioids) it is necessary to **investigate the performance** of the oral modified release formulation **under these conditions**

5.1.4.2. Gastro-intestinal function

- 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** (see also section 5.1.5.1).

I assume this is more easily performed during the clinical study required to show therapeutic equivalence

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**

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

- 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**

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

- **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 (i.e. at delayed gastric emptying) with a subsequent **absorption** of the released dose **once the gastric content is emptied**

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

- As this unintended increased exposure is **not related to a definite product failure causing uncontrolled release**, **dosing recommendations** with regard to e.g. concomitant food intake 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 induce dose dumping**
- For such formulations, **in vitro studies** of the release in alcohol solutions should be performed

See the Q&A document of the QWP in the web page of the EMA

Effects of alcohol

- 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**, an **in vivo** study could be **accepted**, in order to **substantiate** that such an interaction is **unlikely** to occur **in vivo**

Effects of alcohol

- 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**.

Effects of alcohol

- 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

5.1.5. Other points to consider

5.1.5.1. Special populations

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

5.1.5.3. Multiphasic modified release products

5.1.5.4. Prolonged residence time in the stomach

5.1.5.1. Special populations

- **Different physiological conditions** (e.g. transit times, pH, food intake) in **vegetarian**, **paediatric** and **elderly** patients or in **patients** routinely **taking antacids** 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, 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

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

- 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

- **There are modified release** preparations that have been developed **solely in order to mimic a TID or QID dosage schedule**
- In these cases the plasma concentration - time profile of the **modified** release preparation **should be equivalent with the immediate** release formulation **given in the dose schedule that is imitated unless** comparable efficacy and/or safety is supported by additional clinical data.

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

5.1.5.4. Prolonged residence time in the stomach

- 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

5.2.1. Waiving of therapeutic studies

5.2.2. How to design clinical studies

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**

5.2. Therapeutic studies

- 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.

5.2. Therapeutic 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

5.2. Therapeutic studies

- **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** in case at least one of the following conditions is met:

a) **bioequivalence between the immediate** release **and the modified** release product is **shown in terms of Cmax, Cmin 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**

5.2.1. Waiving of therapeutic studies

b) **bioequivalence** between the immediate release and the modified release product is shown in terms of **Cmax, Cmin and $AUC_{(0-\tau)ss}$ 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**

5.2.1. Waiving of therapeutic studies

c) 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
   - **bioequivalence** between the immediate release and the modified release product is shown in terms of **$AUC_{(0-\tau)ss}$** and
   - **Cmax,ss** for the MR formulation **is below or equivalent** to the Cmax,ss for the approved formulation and
   - **Cmin,ss** for the MR formulation **is above or equivalent** to the Cmin,ss for the approved 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, **if** such a **claim** is made

5.2.2. How to design clinical studies

- 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)

5.2.2. How to design clinical studies

- 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 exceptional cases only, where the mechanism of action is the same between indications, an **extrapolation can be made to indications** other than those investigated in the trial, **if** it is appropriately **justified** by the applicant.
  - In cases when the **prolonged therapeutic activity may alter the safety** profile of the drug **during chronic dosing, safety studies may be required**.

5.2.2. How to design clinical studies

- 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**

5.2.2. How to design clinical studies

- 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

5.2.2. How to design clinical studies

- 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**

5.2.2. How to design clinical studies

- Such equivalence and non-inferiority studies **may include** a **placebo arm beside the immediate and modified** release preparations
- 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 my opinion PLACEBO is useless to give the necessary assay sensitivity if any strength is clearly superior to placebo but later all strengths are the same efficacious

5.2.2. How to design clinical studies

- 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.

5.2.2. How to design clinical studies

- **When superiority is claimed** it has to be **proven with clinical trials**.
- Applicants are referred to the scientific guidance documents relevant to the concerned therapeutic area.
- **If** a claim is made for **fewer systemic adverse reactions** for the modified release form, **this has to be substantiated**.

Thank you very much for your attention!