



EUROPEAN GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Session 4 : Line Extension of Immediate Release Products

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1

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This presentation and session are aimed at facilitating a common interpretation of the guideline requirements and the presentation and session should not be interpreted as regulatory requirements. The contents of this presentation and session are subject to changes and should always be seen in conjunction with more recent official EMA and CMD(h) publications and decisions on the matter



1. Total systemic exposure (1/2)

Section 5, pages 9-10:

"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".

and

"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"



1. Total systemic exposure (2/2)

Is total similar systemic exposure for oral dosage forms assessed based on AUC:

- After single dose administration of IR and MR products (with dose correction)
- Within dosing interval of MR formulation after single dose, or in case of accumulation multiple dose administration

Please clarify if total systemic exposure is assessed based on parent and active metabolite(s) or if other metabolites should also be measured.

If total systemic exposure of new MR product is covered by earlier toxicological studies, additional toxicological tests should not be required - even if there are significant differences in total exposure between IR and MR formulations.

It is understood that additional pharmacological or clinical studies to characterize intrinsic properties of DS will not be required unless significant differences - i.e. level of magnitude - in total exposure are observed.

Can earlier studies/published data on total systemic exposure data of IR product be used or are direct comparison data required?



2. Parent and metabolites (1/2)

Section 5.1, page 10:

*"The studies are based on concentration measurements of the active substance **and/or** metabolite(s) [...]. Due to the substantial formulation impact the requirements about metabolites given in the "Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)" is not applicable in this case. Active metabolites should be measured since a change in absorption rate or route of administration may modify the extent and pattern of metabolism"*

Section 5, page 10:

„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."



2. Parent and metabolites (2/2)

Is active metabolite measurement considered sufficient for medicinal products containing inactive prodrugs (i.e. does inactive parent not have to be measured)?

(Active) parent and active metabolite(s) should be measured in case of medicinal products containing active substance which is metabolized to among others active metabolites

- Are there any situations where inactive metabolites should be measured in studies assessing modified release characteristics of the formulation?

We would like to confirm that metabolic profile characterization is not required for products with same route of administration



3. Fasted conditions - non profiling days (1/2)

Section 5.1, page 10:

"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 hours fast after dose) should in general be used on the day of profiling"

Section 6.1.1.2, page 10:

„Fasting conditions in a multiple dose study need to be adapted to realistic situations, i.e. morning administration requires a 10 hour fasting interval whereas for all other administrations 4 hour fasting prior to administration is sufficient. Fasting after each administration should be defined as 2 hours minimum"



3. Fasted conditions - non profiling days (2/2)

During dosing to steady state “worst-case” conditions are required on the days of profiling.

Please clarify what food intake conditions are considered appropriate throughout the rest of the study if the SmPC recommends intake in the fasted state (without specifying time frame) or irrespective of food.



4. Rate and extent of absorption (1/2)

Section 5.1.1, page 11:

„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“



4. Rate and extent of absorption (2/2)

Is a steady state evaluation sufficient when single dose studies can neither be performed in healthy volunteers (e.g. safety reasons) nor in patients (e.g. ethical reasons)?

Is comparison with historical data (IR) sufficient when single dose studies after MR product administration are feasible?

If direct comparison with a single dose of MR product is needed and feasible - should IR formulation be administered as a single dose or as multiple doses within the modified release product dose-interval (single dose of MR product)?



Section 5.1.1, page 11:

„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”



5. Fluctuation (2/2)

Please confirm that in the repeat dosing study the products should be administered according to their approved (IR) and intended (MR) dose intervals

Is this requirement applicable to oral dosage forms or also new routes of administration (e.g. LAIs)?

For oral dosage forms it is assumed that the comparison should be performed over an intended dose interval of the new MR product.

In case the requirement is considered applicable to non-oral long acting products - what is the suitable period of direct comparison?

What acceptable statistics should be used to assess similarity of fluctuation?

- % PTF $[C_{max\ ss} - C_{min\ ss}] / C_{av\ ss}$
- Other parameters



6. Inter-individual variability (1/2)

Section 5.1.2, page 11:

*„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 for the modified release formulation should **preferably** not exceed that for the immediate release formulation unless it is adequately justified in terms of potential clinical consequences”*



6. Inter-individual variability (2/2)

Is inter-individual variability considered as stand-alone criterion?

Reduction of inter-subject variability is not typically the goal of MR formulation development.

Higher inter-subject variability of pharmacokinetic parameters should not prevent product registration if other intended product characteristics are achieved (e.g. within-subject reduced fluctuation or decreased administration frequency)

The proposed ceiling criteria (inter-subject variability not higher than) is potentially too strict. Clinical efficacy and safety studies are required for new MR formulation (except pulsatile release products), therefore the foreseen adequate justification of clinical consequences should typically be possible.



7. Food effect assessment 1 (1/2)

Section 5.1.4.1, page 13:

„For the assessment of food effect besides AUC and Cmax, 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.“



7. Food effect assessment 1 (2/2)

Please provide the rationale for deeming AUC and Cmax not sufficient for assessment of food effect. It seems that this requirement would only be applicable to products where the shape of the concentration-time profiles is claimed important for efficacy or safety based on clinical data.

Please explain how the shapes of the curves should objectively be compared

Please comment if qualitative/descriptive assessment of individual curves is considered appropriate for shape verification in this context?



8. Food effect assessment 2 (1/2)

Section 5.1.4.1, page 12:

*“In case of known clinically relevant 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.”*



8. Food effect assessment 2 (2/2)

Please clarify if the statement “could be useful” indicates an option to the applicant or a strong recommendation.

Food effect study results of the new MR formulation can be compared with historical/published data of food effect of an IR formulation irrespective of whether clinically significant food effect was observed for the IR formulation or not. Studies assessing food effect of the MR formulation and comparing IR and MR formulation under fasted administration should provide sufficient information.



9. ETOH-induced dose-dumping (1/4)

Section 5.1.4.3, page 13:

„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“

*„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**“*



9. ETOH-induced dose-dumping (1/4)

Section 5.1.4.3, page 13:

„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“



9. ETOH-induced dose-dumping (2/4)

What constitutes a reasonable amount of alcohol?.

- Tests should reflect usual drinking habits and not excessive drinking: 1 or 2 units possibly provide adequate characterization of most typical exposure situations

What are the criteria in the assessment of ETOH-induced dose dumping

- Clinical considerations (NTIs vs non-NTIs)
- Mean change vs individual responses (range of values)



9. ETOH-induced dose-dumping (3/4)

EMA Review of MR opioid medicines (EMA/728909/2010)

- „When these capsules were put into a 20% alcohol solution, 80% of the active substance was released within 15 minutes. This means that almost a full day’s dose of morphine would be released all at once” [...]. Therefore, the Committee recommended that the marketing authorisations for these medicines should be suspended

FDA ACP meeting, October 2005

- Risk-benefit of a product containing hydromorphone judged unfavorable
- Co-ingestion of the product with 240mL of 40% alcohol resulted in, on average, 6-times greater peak concentrations with one subject experiencing a 16-times increase

9. ETOH-induced dose-dumping (4/4)

In vitro methods appear sufficiently discriminative
 In vivo data need to be assessed in clinical context

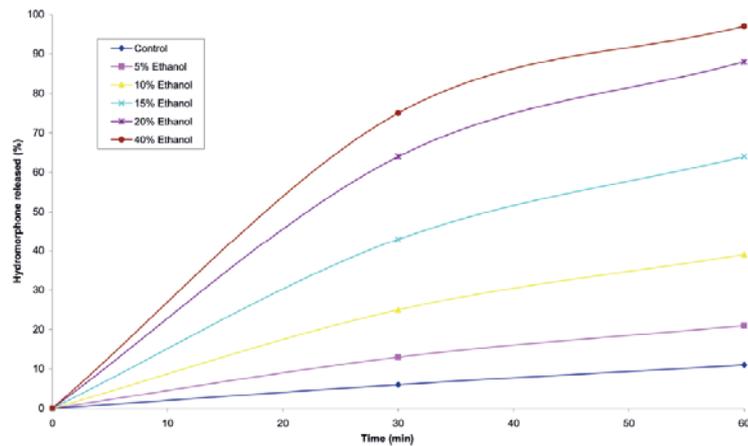


FIGURE 1. Cumulative release of hydromorphone from hydromorphone once daily capsules in simulated gastric fluid/ethanol.

TABLE 1

The Effect of Different Concentrations of Ethanol on Systemic Exposure to Hydromorphone After Administration of 12 mg in Hydromorphone Once-Daily Capsules

Ethanol Concentration (% v/v)	Mean C_{max} Ratio (and range) (Relative to Control No Ethanol)	Mean AUC Ratio (and Range) (Relative to Control No ethanol)
40	5.53 (0.77–15.8)	1.26 (0.61–3.35)
20	1.89 (0.76–5.72)	0.96 (0.41–1.46)
4	1.06 (0.73–1.96)	1.00 (0.48–1.85)



10. Different physiological conditions (1/2)

Section 5.1.5.1, page 14:

„Different physiological conditions (e.g. transit times, pH, food intake and type of food) 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“



10. Different physiological conditions (2/2)

The practical expectation of this general statement is unclear. Routine performance of pharmacokinetic studies in all these special patient groups is considered impractical.

Some of these effects (pH) can be tested in vitro

Should different type of foods be tested only if significant food effect is seen after high-fat meal administration?

Assessment in different patient populations is likely to be addressed in nested studies within pivotal safety and efficacy studies.



Questions from attendants

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Section 5, page 9:

*“The applicant has to **prove** that the benefits of the new formulation outweigh the potential risks (e.g. medication errors) linked with this product.”*

Please clarify with an example of what type of data would be considered as sufficient proof in this context?

Particularly in the case of risk of medication error, are risk minimization strategies in the labelling and product physical attributes sufficient, or evidence is required from post marketing experience.



12. Dosing Recommendations

Section 5.1, page 10:

*„In terms of concomitant food intake, the multiple dose bioavailability study should be performed under the **SmPC** labelled condition [...].”*

The text in the guidance implies that in comparative multiple dose studies SmPC recommendations of the reference product (e.g. IR) should be applied to new MR product.

Can the trial be performed with each product administered according to its desired dosing with respect to food to demonstrate potential advantages of the new product, or should potential benefits with respect to food intake be only addressed in a single dose studies as implied in Section 5.1.4.1 and PK equivalence at steady state must be demonstrated in the SmPC conditions of the IR product?