



17 October 2019  
EMA/CHMP/536342/2019

## Outcome of public consultation on 'EMA DRAFT Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CHMP/EWP/280/96 Rev1)

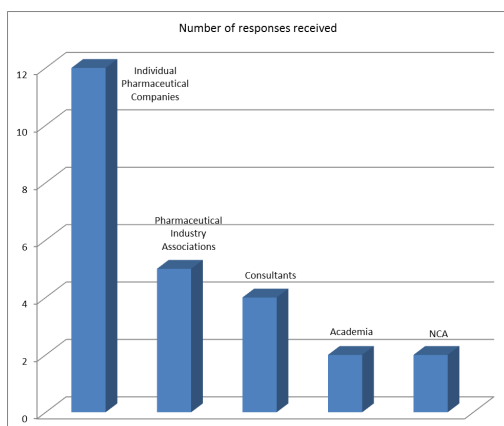
Summary report of comments received during the public consultation and next steps

### 1. Background and consultation

The EMA Draft 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CHMP/EWP/280/96 Rev1) was published for public consultation from 15 March 2013 to 15 September 2013. Following the consultation the guideline was updated to take into account the comments received and a final version was published on 27 November 2014. The present document is a high-level overview of the comments received and adds more detail on how EMA addressed these. Note that the text in the final guideline takes precedence over any statements in the present document.

### 2. Contributors

The largest group of contributors was individual pharmaceutical companies, followed by pharmaceutical industry associations. Consultants, academia and national competent authorities were also represented among the contributors. The distribution of contributors is given in the graph below:



### 3. Summary of main points raised during the consultation

The majority of the comments expressed by the stakeholders were related to the need for clarifications in several sections, but also some perceived divergent views from contributors were received. The comments received are divided into three major areas in line with the modified release guideline structure, i.e. modified release (MR) dosage forms of (1) a new chemical entity, (2) an already authorised formulation with a different release rate (3) abridged applications for modified release forms referring to a marketed modified release form.

#### **3.1. Applications for modified release dosage forms of new chemical entities**

This section was largely supported by stakeholders. However, some clarifications were proposed and accepted (e.g. it was clarified that this section is only applicable to a New Chemical Entity (NCE) *initially* developed as a MR formulation and also reference to clinically *relevant* food effect was introduced). The recommendation on using the MR formulation in DDI (drug-drug interaction) studies was not agreed by responders, but EMA's position is that it is preferred, if feasible, that DDI studies are performed using the MR formulation. Several comments were received on the need for clarification on IVIVC (*in vitro in vivo* correlation) on transdermal drug delivery systems and for IM/SC (intramuscular/subcutaneous) formulations. No change was made in the IVIVC section as EMA considers that the development of IVIVC is the applicant's decision and for this purpose the level of general guidance currently provided is adequate. EMA has clarified in the related Appendix III that an IVIVC is only expected to be developed in the specific case when formulation controls the rate of drug appearance in plasma. A better description of the requirements for the evaluation of the patch adhesion and improved descriptions of the kinetic conditions for IM depot formulations were included in the final version in response to comments received.

#### **3.2. Application for a modified release formulation of a drug that is authorised in a formulations with a different release rate**

For [Section 5.1 Pharmacokinetic studies](#), several comments were received on the need for clarification on multiple-dose studies. To address these, EMA provided clearer definitions on how to judge a lack of accumulation and the requirement for multiple-dose studies, as well as on the conditions to be considered regarding concomitant food administration when multiple-dose studies are performed. It was specified that multiple-dose studies are only requested when drug accumulation is observed.

Regarding the definition of the pharmacokinetic parameters chosen for comparison between IR (immediate release) and MR products, EMA clarified that parameters referred to are to be understood as proposed and it is the Applicant's responsibility to justify the most relevant parameters based on knowledge of the exposure-response for efficacy and safety for the intended medical product. A clarification was included on the need to also monitor plasma levels of active metabolites. Although comments were received opposing the necessity and relevance of comparing inter-individual variabilities between the IR and MR formulations, EMA considers this a relevant variable to characterise as it may impact the benefit-risk balance. Regarding dose proportionality, comments for clarification were received focusing on the need for multiple-dose studies and several stakeholders proposed that these studies should only be undertaken when PK is known to be non-linear. However, EMA considers that both single and, in case of accumulation, multiple-dose studies are required for evaluating dose proportionality.

Regarding the influence of food on the bioavailability of oral MR formulations, EMA emphasised that this should be studied after single dose administration. Comments were received on the need for a 4-

way cross-over study with the IR and MR formulations with and without food when there is a known clinically relevant food effect and on the need for comparisons on the shape of the concentration-time profiles. In this aspect EMA considers that a 4-way cross-over study could be useful to quantify the food effect on each formulation and that the shape of the curve could be important for benefit-risk evaluation, and therefore these requirements were maintained in the final version. EMA confirmed that, if the product is commonly co-administrated with active substances affecting the GI physiology and function, this condition should also be investigated, since gastro-intestinal conditions can influence the performance of MR formulations.

Regarding the effect of alcohol, comments received concerned the lack of defined alcohol limits (*in vitro* and *in vivo*) to be investigated. EMA decided not to specify limits for the amount of alcohol since defining general rules is not possible and accordingly Applicants are requested to justify the chosen approach.

In Section 5.2 Therapeutic studies, it was proposed by several stakeholders to consider the need for clinical efficacy and safety studies as an exception, instead of a norm. EMA does not agree to this, but an improved explanation on the possibility to waive these studies was provided in the final version. It was clarified that only one of the three possible proposed conditions needed to be fulfilled in order to waive clinical therapeutic studies. Regarding the design of clinical studies, EMA clarified that clinical superiority is only needed to be shown if this is the claim for the MR formulation. EMA also explained that only in exceptional cases, if the mechanism of action is the same, extrapolation between indications can be performed. Finally, some additional requirements on local safety for patches or depot formulations were also included in the final version of the guideline.

### **3.3. Abridged application for modified release forms referring to a marketed modified release form**

Information was added to clarify new requirements for biowaivers; studies in healthy volunteers/patients; bracketing of additional strengths; handling differences in formulation-related food interactions in a condition not recommended in the SmPC. Regarding the latter aspect, several stakeholders commented on the fact that if bioequivalence is not shown in a non-SmPC recommended condition, this should be considered a safety and not an efficacy issue and as such, in some conditions, a difference should still be accepted and a generic be approved. However, EMA considers that fasting and fed studies are designed to simulate the possible extremes in real life practice. For example, a difference obtained in a fed study may also be extrapolated to a scenario where the MR product is taken fasting, but immediately before a meal.

In Section 6.1 Prolonged release oral formulations, several comments on the need for clarification regarding the proposed single dose studies were received. Based on these, the final guideline includes an explanation on the utility of performing a 3-way clinical study (Test<sub>fasted</sub> vs Ref<sub>fasted</sub> vs Test<sub>fed</sub>) in one of the proposed clinical trial options. This can be performed in order to generate intra-individual data to describe a potential food effect. Regarding the requirement of multiple dose studies in abridged applications, conflicting comments were received from stakeholders, both supporting and disagreeing with the necessity of these studies. However, EMA concluded that bioequivalence in multiple-dose studies is an important part of the evaluation of MR products. For generics this includes e.g. the concentration at the end of dosing interval at steady state in order to compare the shape of the profile. Thus, this requirement is maintained in the final version of the guideline. If no accumulation is observed, multiple dose studies may be waived. In this regard, several stakeholders criticised the EMA's proposed criterion that  $AUC_{(0-T)}$  after a single dose should cover more than 90% of  $AUC_{(0-inf)}$  as being too strict. However, EMA considers this limit as appropriate for waiving multiple dose studies. In addition, if it is demonstrated that there is low accumulation and multiple-dose studies are waived,

then additional partial AUC parameters in single-dose must be evaluated for comparison of the shape of the plasma concentration profiles.

Regarding the design of the multiple-dose studies, clarifications on fasting/fed conditions and steady-state evaluation were included in the final guideline following stakeholder comments. Clarifications were also incorporated on the strengths to be evaluated, the acceptability to include patients in multiple-dose studies (in case of safety concerns in healthy volunteers), and on the shape of a single unit formulation as a concern for the acceptance of a biowaiver for a different strength. For multiple unit formulations, the guideline has been simplified, as the required study is only at the highest/most sensitive strength if the different strengths are proportional, with identical beads/pellets and similar dissolution profiles.

In Section 6.2 Delayed release formulations, the acceptance of the highest/most sensitive strength was included in the guideline, since no dosage dependent accumulation is expected for delayed release formulations. EMA considers that multiple-dose studies are not required, as opposed to some stakeholders' comments. The definition of the conditions for subject removal from the statistical analysis, where non-existing or aberrant concentrations profiles are observed after administration of a delayed release formulation in a bioequivalence trial, was updated following several comments and suggestions.

In Section 6.4 Intramuscular/subcutaneous depot formulations, most of the comments received were related to perceived practical difficulties in complying with the general requirements for multiple-dose studies due to long terminal half-life or long dosing intervals. The practical difficulties are acknowledged, but multiple dose studies can only be waived in exceptional circumstances. Scientific Advice can be sought for case-by-case guidance on this topic.

Regarding Section 6.5 Transdermal drug delivery systems, a major revision of the text was done based on comments received. For example, the definition on requirements for the adhesion properties of the patch was improved and an additional appendix (Appendix II in final version) with more in depth guidance was added. The definitions on the requirements for single-dose and multiple-dose studies, as well as on the PK parameters to be evaluated, were also updated in the final version.

Section 6.6 Bracketing approach was updated with references to previous sections where bracketing approaches have been stated.

For Section 6.7 New strength for an already approved MR product, several stakeholders suggested clarifications and these have generally been accepted by EMA and included in the text.

Regarding Section 6.8 Evaluation, stakeholder comments were provided on the proposed non-acceptance of truncated AUC for long half-life drugs, the need for better definition for partial AUC and the need for considering  $C_{max}$  and  $t_{max}$  on all individual phases for multiphasic MR products. Regarding truncated AUC, EMA's position is that a default truncated AUC at 72 h is not acceptable. Regarding partial AUC, EMA considers it is not possible to provide a general rule on the cut-off time points and thus, this is a case by case decision based on the PK profile, e.g. on the respective IR and the MR parts, and should be justified and pre-specified in the study protocol. Regarding multiphasic MR products, EMA considers that  $C_{max}$  in each individual phase is important to confirm the similarity between the formulations and therefore this requirement remains in the final version guideline. Clarification on the use of  $C_{min,ss}$  vs  $C_{\tau,ss}$  was requested to assess the curve shape and EMA recommends that a comparison based on the  $C_{\tau,ss}$  is sufficient in case of generics for this purpose. Based on several comments about the clarity of the requested parameters to be evaluated in the different types of formulations (MR with/without accumulation, Delayed Release, Multiphasic MR), EMA resolved this by including four tables with listings of the required PK parameters for each individual formulation. Finally, some comments were received regarding the possibility of using two consecutive

administrations of the same product after steady-state in a multiple dose trial in order to determine the  $CV_{intra}$  (intra-individual Coefficient of Variation) and this was agreed. EMA also confirmed that a formal statistical evaluation of  $t_{max}$  is not required.

In [Section 6.9 Effects of alcohol](#), some stakeholders commented that the requirements for reformulation of the test formulations (if accelerated release is observed *in vitro* in presence of alcohol) may result in an extra burden on the test formulation that does not apply to the reference formulation. However, EMA has maintained the requirement as proposed in the draft, since if an alcohol effect cannot be avoided and is also present in the reference product, the applicant can choose to address clinical relevance.

### **3.4. Appendices**

#### **3.4.1. Appendix I - sensitisation and irritation test for transdermal products**

After the MR guideline was published, following comments received from stakeholders, an update of Appendix I was published (in June 2018) as an EMA Question and Answers (Q&A) Clinical pharmacology and pharmacokinetics: 8.1 (<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers>). The Q&A addresses the testing of skin irritation and sensitisation for transdermal products and in addition the recommended study designs and scoring systems that are proposed to be used.

#### **3.4.2. Appendix II - in vivo skin adhesion**

Appendix II is new in the final MR guideline. This appendix was moved from the Guideline on quality of transdermal patches (EMA/CHMP/QWP/911254/2011) that was under public consultation from 15 September 2012 to 15 March 2013, i.e. approximately during the same timeframe as the MR guideline. Several stakeholders commented that the appendix did not fit optimally in the quality guideline. EMA agreed and the appendix was therefore moved to the MR guideline.

Several stakeholder comments were received and the section has been restructured and extensively updated. Instead of using a scoring system, adhesion should be measured as the percentage of area that remains adhered at the end of the dosing interval. Clarifications e.g. on the conduct of adhesion studies in healthy volunteers/patients, waiving of additional strengths, acceptance criteria and statistical methods were included. For stakeholder comments see:

[https://www.ema.europa.eu/en/documents/comments/overview-comments-received-draft-guideline-quality-transdermal-patches\\_en.pdf](https://www.ema.europa.eu/en/documents/comments/overview-comments-received-draft-guideline-quality-transdermal-patches_en.pdf).

#### **3.4.3. Appendix III - in vitro in vivo correlation**

Several stakeholder comments were received on the reference formulation and the section has been extensively updated. Details on choice of reference formulation for deconvolution (RFD) for permeability limited MR formulations, IM/SC depot formulations and possible use of physiologically based pharmacokinetic (PBPK) modelling have been added. Furthermore, the importance of including a RFD to support the IVIVC development has been emphasised and explained.

The working process has been clarified, i.e. starting with the simplest model and then increasing in complexity as necessary. Again, the use of PBPK and some considerations for the PBPK model were

highlighted based on comments received. In the final guideline the continuous development to strengthen the evidence supporting the IVIVC is stressed.

#### **3.4.4. Appendix IV summary of study recommendations for abridged applications**

The introduction of tables as a summary of study recommendations was well received. An update was done to include the shape of single unit formulation as an additional consideration for a possible acceptance of a strength biowaiver.

### **4. Next steps**

Following the consultation the guideline has been revised to take comments received into account. The guideline has already come into effect. No further public consultation is foreseen.

### **5. Annexes**

List of contributors and their individual comments is available on the Agency's website at [https://www.ema.europa.eu/en/documents/comments/overview-comments-received-draft-guideline-pharmacokinetic-clinical-evaluation-modified-release\\_en.pdf](https://www.ema.europa.eu/en/documents/comments/overview-comments-received-draft-guideline-pharmacokinetic-clinical-evaluation-modified-release_en.pdf)