25 January 2018
EMA/CHMP/729976/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Paracetamol oral use, immediate release formulations product-specific bioequivalence guidance' (EMA/CHMP/356877/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 4-5, 10-11	1	Comment: It would be advisable to add in the document the range of paracetamol strengths, which are in the scope of this guideline, similarly as it has been proposed for e.g. ibuprofen. Proposed change (if any):	Not accepted. For paracetamol many different immediate release formulations and strengths are authorised. First of all, the heading was getting exponentially long, and most important due to the many different immediate release formulations, it was problematic to cover this formulation by formulation in the specific sections. Therefore the heading only indicates 'oral use, immediate release formulations'. To cover the various immediate release formulations, under 'number of studies and other design aspects' the following is added: "Additional studies may be necessary depending on the formulation in accordance with the Guideline on the Investigation of Bioequivalence (for example orodispersible tablets)".
Bioequivalence assessment, Main PK variables (in the table)	1	Comment: In this section, Tmax is listed as one of the main PK variables (together with Cmax and AUC(0-t)). Could you please clarify if the intention was to make the Tmax one of the primary endpoints of the study? In our opinion, the inclusion of Tmax in the primary endpoint analysis is not justified for paracetamol and should be avoided. According to the "Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr**, the evaluation of Tmax should be performed when the	Not accepted. Indeed, normally t_{max} is not a pivotal variable, unless the rate of absorption is important with regard to for instance efficacy. For paracetamol many different immediate release formulations and strengths are authorised. Amongst them, also formulations with a rapid release, intended to have a fast relief of pain. Therefore t_{max} has been included as a pivotal variable to cover this situation. To be noted, as a basic rule, the Guideline on the Investigation of Bioequivalence, should be followed, and thus the use of t_{max} as pivotal variable is only applicable in certain situations.

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		rapid release of the substance is clinically relevant and of importance for the onset of action or is related to adverse events (AE). Rapid onset of action is usually of importance for life-saving products, and paracetamol is not one of those. Also, there is no data that any AEs could be related to the rapid release of the substance from the formulation. Therefore, for a standard pain-killer like paracetamol, in immediate release oral formulations, it is recommended to keep the requirements as they are presented in the abovementioned guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**, that is the statistical evaluation of Tmax should not be required. Proposed change (if any): Main pharmacokinetic variables: Cmax, AUC(0-t)	
Bioequivalence assessment, 90% confidence interval (in the table)	1	Comment: In this section, it is proposed that the median and range for Tmax should be “comparable”. On the other hand, as it was stated above, the principle “Guideline on the investigation of bioequivalence”, CPMP/EWP/QWP/1401/98 Rev.1/Corr** states that in general, the statistical evaluation of Tmax is not required. Could you please clarify in this section how the applicants should demonstrate the comparability of Tmax, if, at the same time, statistical evaluation of this parameter is not required.	Not accepted. Indeed, normally t_{max} is not a pivotal variable, unless the rate of absorption is important with regard to for instance efficacy. For paracetamol many different immediate release formulations and strengths are authorised. Amongst them, also formulations with a rapid release, intended to have a fast relief of pain. Therefore t_{max} has been included as a pivotal variable to cover this situation. To be noted, as a basic rule, the Guideline on the Investigation of Bioequivalence, should be followed, and thus the use of t_{max} as pivotal variable is only applicable in certain situations. In case the before mentioned

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		Proposed change (if any):	example is not applicable, statistical evaluation of t_{max} is not required.
Line 17	2	Comment: Currently a PK study is suggested if “the biowaiver is not feasible or applied”. It would be helpful to point out that since paracetamol is a Class 1 drug, a biowaiver approach can be considered. Proposed change (if any): “As paracetamol is classified as a BCS Class1 drug, the biowaiver approach to product approval can be considered. However, if dosage form requirements or dissolution behaviour are unable to meet the Biowaiver criteria, a pharmacokinetic study can be conducted.”	Not accepted. As a basic rule, the Guideline on the Investigation of Bioequivalence, should be followed. In this product specific guidance, additional information is provided on the BCS classification for paracetamol being a Class I drug. Although this implies that paracetamol is eligible for a BCS based biowaiver, an applicant may always submit an *in vivo* bioequivalence study, also in case the formulation and dissolution criteria would have fulfilled the BCS based biowaiver criteria. In addition, if these criteria would not be fulfilled, automatically it is expected that an applicant submits an *in vivo* bioequivalence study. It is considered that the text 'in case a BCS biowaiver is not feasible or applied' is sufficiently clear to cover this.