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EMA/CHMP/116717/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'draft sorafenib product-specific bioequivalence guidance' (CHMP/PKWP/EMA/423707/2013)

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

Stakeholder no.	Name of organisation or individual
1	EGA
2	MEB, The Netherlands

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The EGA welcomes the opportunity provided by the EMA PKWP to comment on the proposed product-specific bioequivalence guidelines and generally on the approach to product specific guidance for bioequivalence. EGA member companies are generally supportive of this approach and take this opportunity to provide comments on some product specific proposals as well as to reiterate points raised in the context of the public consultation on the concept paper as those have not yet lead to clarifications from the EMA PKWP.	Accepted. Per standard procedure it is not foreseen to publish the overview of comments for the Concept Paper "Development of product-specific guidance on demonstration of bioequivalence" (EMA/CHMP/423137/2013).
	Timing of the guideline availability The timing of issuance of a product-specific guideline is of great importance to the generic pharmaceutical industry. The EGA recommends that for future molecule prioritisation, a period of minimum 3 (to 5) years before data exclusivity expiry (i.e. minimum 3 (to 5) years before 1st possible MA submission) is considered for the final product specific guideline to be available. For the guideline to be useful in practice, it needs to be available very early in the development process. Even more so, a late publication would not only be of limited value but would also possibly translate as an additional hurdle for those companies having engaged (and invested significant resources into study planning and possibly study conduct) in such pharmaceutical developments well in advance of data exclusivity (and patent) expiry, which is undesirable. The concept paper and specific product guidelines when final should also include a statement allowing the submission and assessment of other approaches to establishing bioequivalence, safeguarding predictability of the regulatory outcome particularly for	Products are selected upon CMDh recommendation bi-annually. A set rule for the timing of the publication cannot be established. Furthermore, product-specific BE guidances should not be understood as being legally enforceable and are without prejudice to the need to ensure that the data submitted in support of a marketing authorization application complies with the appropriate scientific, regulatory and legal requirements.

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	bioequivalence studies which may have been completed prior to the development of the product-specific guidance, provided they are scientifically sound. As consultation is also foreseen for each product-specific guideline, this also needs to be taken into account in the guideline elaboration process.	
	Prioritisation of products for bioequivalence guideline development – criteria and process Although a first layer of prioritisation (IR vs MR) seems envisaged, the draft concept paper does not describe the chosen procedure for the selection of products for which bioequivalence guidelines will be developed. We recommend that the EMA PKWP exposes in transparency the criteria or triggers which will lead to such guidance document development (e.g. request to the agencies on certain products, timing of data-exclusivity expiry, market value).	Products are selected upon CMDh recommendation bi-annually.
	Convergence with existing or planned product-specific bioequivalence guideline in other regulatory regions The draft concept paper does not refer to the foreseen EMA PKWP approach where other regulatory authorities (e.g. US FDA) already have in place the product-specific approach to bioequivalence and as such, a list of priority products for which such guidelines will be developed. Given the number of initiatives on regulatory convergence or collaborative efforts on generic medicines dossier assessment among different jurisdictions, we would encourage dialogue and where possible a pragmatic collaboration in order to mutualise efforts and prevent duplication. For EU operators, it would be highly undesirable and counter-	The comment has been acknowledged; however, this is currently not foreseen.

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	productive that two (or more) divergent guidelines would be adopted by different regulatory jurisdictions for the same medicinal product.	
	Scope of the product-specific guidelines and complicated formulations In comparison to IR products, bioequivalence testing of MR products is much more complicated and strongly depends on the specific properties of the individual products that cannot be properly addressed in a guideline of general character. In fact guideline CHMP/EWP/280/96 Rev 1 currently under revision leaves many topics and questions unaddressed or unresolved which could be in a second step, properly addressed in product-specific guidelines thus providing the necessary flexibility to properly cover specific situations.	Accepted.
	Safeguarding scientific approaches to complex pharmaceutical development and technologies Based on the experience and successful development of initial guidance documents for immediate release products, it will be necessary to assess whether for modified release products, a similar approach can be suitable. The EMA PKWP should prevent product-specific guidelines for MR products (if and when included) to impact on the choice of a given technology, especially as these evolve constantly. Indeed, a number of proprietary technologies with unique characteristics and product-specific recommendations are entering into play when it comes to modified release products. We therefore call on a careful assessment of any recommendation made on design elements, as these should not preclude other approaches where scientifically justified.	Accepted.
	Clarifying application of BCS class 1 biowaiver The EGA would welcome clarity on those products where a BCS class 1 biowaiver could be accepted.	Accepted.

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	Experience shows significant disharmony in the approach to BCS biowaiver between the EU Member States. Providing product-specific advice will promote a harmonised interpretation, facilitate review and assessment as well as prevent referrals. The current proposed layout should allow a distinction between the actual 'BCS classification' on the one hand and the 'eligibility for BCS based biowaiver' as the latter can differ based on specific molecule properties.	
	Biological media For the choice of biological media for the measurement of analyte concentration, the choice of plasma should be modified to say plasma/serum in order to account for the situation where serum can also be used.	Accepted.
	References and Sources of Information For clarity purposes, the EMA PKWP is asked to clearly reference and source the information on which the product specific bioequivalence guidelines are established, particularly for off patent molecules where several MAs are available already. For such off-patent molecules, it is important that not only information from the originator applications are considered but also that of subsequent generic medicines applications.	Accepted. The basis for the recommendations is described in the "Compilation of individual product-specific guidance on demonstration of bioequivalence" (EMA/CHMP/736403/2014)
	Impact Assessment and Practical Implementation for existing studies/registrations Section 7 of the concept paper was entitled 'Impact assessment' and was extremely concise. Given the first 17 selected molecules, it appears that some are still under patent while others already have generic medicines registered/on the market. It is not clear what the consequence of these product specific guidelines will be on already registered products and particularly in	As the standard procedure foresees, final guidances will enter into force 6 months after they are adopted by the Committee for Medicinal Products for Human Use.

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	situations where new or repeat use procedures will be initiated referencing to bioequivalence studies performed before product specific guidelines were published as draft or final texts. Formal and clear guidance regarding the practical aspects of the implementation of these product specific guidelines would certainly contribute to promoting a harmonised implementation by assessors throughout the EU and also to ensuring predictability in registration procedures (ie, avoiding unnecessary delays) as well as consistency of assessments. The EGA would like to propose that the implementation plan covers for situations where bioequivalence studies/programmes are either: ▪ completed or initiated before adoption of the final revised guidance and, ▪ started after adoption of the final revised guidance. In all these instances, the EGA proposal aims at preventing the unnecessary repetition of well-designed studies or unnecessary delay in generic medicine development (or registration) linked to the uncertainty surrounding the final outcome of the revision of the guideline The EGA recommends that: ▪ The final guidelines enter into force within a 6 month period following their adoption by the CHMP (transition period) as the general practice foresees. ▪ The documented date of the submission of the study protocol to the IEC/IRB and Competent Authorities for approval of the study should be the defining date in determining whether the product specific guidelines would apply	

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	▪ All studies for which the submission of the study protocol for approval took place after publication of the adopted final text should be compliant with the provisions laid out in the final guidelines. ▪ For studies or study programmes where the submission of the study protocol to the IEC/IRB and Competent Authorities for approval of the study took place before final adoption and publication of the guideline, regulatory acceptance should be considered. Companies have carried out or are carrying out today studies for medicinal products which will be submitted in MA applications before or around the time of adoption of the final guidance documents. It is important to clarify upfront regulatory expectations for these studies.	
2	1. Some APIs are stated as BCS Class I or III (e.g. sunitinib, Emtricitabine/tenofovir disoproxil, etc.), and also requirements for BE study are stated. It is unclear if the meaning is this API is not qualify for BCS-biowaiver. 2. Maybe add one row of “remarks for biowaiver”? information for additional strengths, BCS-biowaiver, and solution with sorbitol (e.g. Oseltamivir) can put here. 3. Background is written differently for the same statement in BCS and strength. 4. With regards to API with unknown BCS, should we give recommendations for biowaiver? We have seen “The available data on solubility does not allow the BCS classification of oseltamivir. If the Applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, a BCS biowaiver could be applicable.” This recommendation never appears with other APIs under the same conditions.	1. Accepted. 2. The comment has been acknowledged; however, this is addressed in the guideline, therefore no further action is needed. 3. Accepted. 4. As it is neither BCS Class I nor BCS Class III, a BCS biowaiver is not possible.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	1	**Comment:** We believe there is an inconsistency in the following paragraph which needs to be corrected in the final guideline. ***"There is only one strength available i.e. 200 mg****. Sorafenib exhibits non-linear pharmacokinetics with a less than dose-proportional increase in AUC with increasing doses within the dose range 400-800 mg. The non-linearity is proposed to be due to limited solubility.* ***Hence, the highest and the lowest strength should be studied."***	Accepted.
background	2	**Comment:** Hence, the highest and the lowest strength should be studied. **Proposed change (if any):** As there is only one strength 200 mg, the last sentence should be deleted.	Accepted.