21 May 2015
EMA/CHMP/116836/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'draft sunitinib product-specific bioequivalence guidance' (CHMP/PKWP/EMA/423716/2013)

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

Stakeholder no.	Name of organisation or individual
1	MEB, The Netherlands
2	Pharmaceutical Research Institute (Instytut Farmaceutyczny), Warsaw, Poland Piotr Rudzki, Ph.D.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	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. Accepted.
2	1. The Pharmaceutical Research Institute (PRI) is pleased to have the opportunity to comment on the draft Product-Specific BE Guidance released by the EMA. PRI is a R&D organisation designed for comprehensive technology development and commercialization of medicinal products (API synthesis, drug dosage form, analytical services, registration). PRI has over 60 years of experience in the field of pharmaceutical R&D. Pharmacology Department of PRI conducts GLP compliant pharmacokinetic studies, including bioavailability and bioequivalence.	1. Not accepted. These guidances only provide critical design aspects. There is always variability; therefore it is not considered feasible to include more details due to uncontrolled aspects. 2. Not accepted. EMA has tried to reduce the size of each product-specific guidance. The first cover page has to be

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	The general idea of a product specific bioequivalence guidance is definitely a good proposal, which will facilitate both preparation and evaluation of drug registration documentation. The presentation of data in the form of table greatly facilitates reading. However, it would be appreciated if some more details, e.g. number of subjects and sampling schedule, would be suggested as the EMA proposal, which may be changed by the Applicant in specific cases. 2. Product specific BE guidelines issued by FDA are usually documents of one page only. As title page and information contained in the EMA guidance are more detailed it seems that 2-page document would be both sufficient and in-line with environmental-friendly policy.	kept as for all EMA guidelines/guidances.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Strength	1	**Comment:** Also a lower strength may be used **Proposed change (if any):** strength: 50 mg (the highest strength) or lower strengths	Accepted.
15	2	**Comment:** It would facilitate reading if the whole table "Requirements for bioequivalence demonstration" was placed on a single page. The first column seems to be wider than necessary and vertical alignment could be better than horizontal. **Proposed change (if any):** Whole table "Requirements for bioequivalence demonstration" is placed on a single page.	Not accepted. The EMA template has to be followed.
15	2	**Comment:** Two empty rows in the table seem to be unnecessary ("BE study design", "Analyte"). **Proposed change (if any):** Delete empty rows.	Accepted.
15	2	**Comment:** Table, row "Bioequivalence assessment" The acceptance criteria for 90% confidence interval: 80.00 – 125.00 are missing "%". **Proposed change (if any):**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"80.00 – 125.00" should be replaced by "80 .00 – 125.00%"	
15	2	**Comment:** Table, row "Bioequivalence assessment" The acceptance criteria for 90% confidence interval: 80.00 – 125.00% indirectly indicate that sunitinib is not considered by the EMA as a narrow index drug nor as a highly variable drug. It would be appreciated if both information on sunitinib status would be stated *expressis verbis*. **Proposed change (if any):** New row in the table entitled "Special status" with checkboxes for "Narrow therapeutic index drug" and "Highly variable drug/product"	Not accepted. The comment has been acknowledged; however, no changes will be implemented since an acceptance criteria for 90% confidence interval of 80-125% already infers exclusion from narrow therapeutic index. Moreover, the footnote states that whether the substance is highly variable has not been reviewed in relation to the product-specific bioequivalence guidance.