1 April 2015
EMA/CHMP/116042/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft imatinib product-specific bioequivalence guidance' (CHMP/PKWP/EMA/423733/2013)

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

Stakeholder no.	Name of organisation or individual
1	Novartis Pharma AG
2	SciencePharma (Poland)
3	MEB, The Netherlands
4	Pharmaceutical Research Institute (Instytut Farmaceutyczny), Warsaw, Poland Piotr Rudzki, Ph.D.
5	EGA

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

© European Medicines Agency, 2015. Reproduction is authorised provided the source is acknowledged.

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Novartis welcomes the opportunity to comment on Draft imatinib product-specific bioequivalence guidance. Based on Novartis's experience with Glivec (imatinib, Novartis Brand), we suggest conducting the bioequivalence studies under both fasting and fed conditions. The rationale to conduct the study under both fasting and fed conditions is because Glivec showed some food effect, though minimal, 7.4% decrease in AUC with a high fat meal vs. fasting conditions. Any further decrease in AUC will likely become clinically significant, which could be a result from different excipients and excipients-food interactions in a generic product.	The comment has been acknowledged. However, the "Investigation of bioequivalence" guideline (CPMP/EWP/QWP/1401/98 Rev. 1) will be followed.
3	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	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.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	under the same conditions.	
4	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. 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. 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.	Accepted.
5	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	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).

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	lead to clarifications from the EMA PKWP.	
	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 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.	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.
	Prioritisation of products for bioequivalence guideline development – criteria and process Although a first layer of prioritisation (IR vs MR) seems envisaged,	Products are selected upon CMDh recommendation bi-annually.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	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).	
	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-productive that two (or more) divergent guidelines would be adopted by different regulatory jurisdictions for the same medicinal product.	The comment has been acknowledged; however, this is currently not foreseen.
	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	Accepted.

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

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

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

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	or around the time of adoption of the final guidance documents. It is important to clarify upfront regulatory expectations for these studies.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table, right column, fourth row from the top (*BE Study design, either fasting or fed*)	2	**Comment:** There is a statement, that study under fasting conditions is preferred. A fed study is **acceptable** according to the Guideline on the investigation of bioequivalence based on SmPC recommendations. However, according to the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) "*for products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study **should** generally be conducted under fed conditions".* There seems to be a contradiction between the two guidelines. Should the Guideline on the Investigation of bioequivalence be interpreted in a way that where SmPC recommends *intake of the reference medicinal product only in fed state,* conducting BE study in the fed state is mandatory? Or can it be assumed, that fasting study is generally recommended for investigation of BE regardless of SmPC recommendations, while fed study is an option that can be taken into consideration by the applicant? **Proposed change (if any):**	This product specific guidance only refers to the requirements for bioequivalence demonstration for Imatinib. The acceptance of studies under either fed or fasting conditions for imatinib are clearly explained. Clarification of the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) is out of the scope of this document.
Study Design	3	**Comment:** Food intake does not affect bioavailability of imatinib. The risk of gastrointestinal irritations is limited in single dose BE study. Therefore we consider to accept	Acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		BE only under fasting conditions **Proposed change (if any):**	
15	4	**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.	Acknowledged; however, the design of the table will not be changed.
15	4	**Comment:** The grey background of table seems to be unnecessary and may be considered not environmental-friendly due to increased consumption of printing consumables. **Proposed change (if any):** The background of table should be white.	Accepted.
15	4	**Comment:** Two empty rows in table seem to be unnecessary ("BE study design", "Analyte"). **Proposed change (if any):** Delete empty rows.	Accepted.
15	4	**Comment:** Table, row "Bioequivalence assessment" Literature data suggests that imatinib is not a long half-life drug (Parrillo-Campiglia et al., 2009; Jawhari et al., 2011; Nikolova et al., 2004; Peng et al., 2005).	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Sampling time of 72 hours should be sufficient to obtain AUC0-t > 80% AUC0-inf for at least 80% of subjects as required by the EMA Bioequivalence Guidance CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. In many subjects even shorter sampling period will be sufficient. Therefore, determination of imatinib concentration at sampling time of 72 hours seems to be not always necessary. Summing up, AUC0-t might be more suitable pharmacokinetic parameter than AUC0-72h. **Proposed change (if any):** Main pharmacokinetic variables: AUC0-72h, AUC0-t, Cmax	
15	4	**Comment:** Table, row “Bioequivalence assessment” The acceptance criteria for 90% confidence interval: 80.00 – 125.00 are missing “%”. **Proposed change (if any):** “80.00 – 125.00” should be replaced by “80 .00 – 125.00%”	Accepted.
15	4	**Comment:** Table, row “Bioequivalence assessment” The acceptance criteria for 90% confidence interval: 80.00 – 125.00% indirectly indicate that imatinib 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 imatinib status would be stated expressis verbis.	The comment has been acknowledged; however, no changes will be implemented since an acceptance criteria for 90% confidence interval of AUC of 80-125% already infers exclusion from narrow therapeutic index.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): New row in the table entitled “Special status” with checkboxes for “Narrow therapeutic index drug” and “Highly variable drug/product”	
16	4	**Comment:** It would be appreciated if guidance indicated possibility of claiming highly variable drug status. According to available data (Parrillo-Campiglia et al., 2009; Jawhari et al., 2011; Nikolova et al., 2004; Peng et al., 2005) imatinib does not belong to highly variable drugs. **Proposed change (if any):** As drug variability has not been reviewed, this guidance is not applicable to highly variables drugs. Imatinib seems not to be a highly variable drug. However, in case tested product is proven to be a highly variable product it, should be confirmed by the Applicant at time of submission.	Acknowledged; however, no changes will be implemented because the approach for Highly variable drugs is defined for all products in a footnote.
	5	**Comment:** Based on the originator product SmPC, the half-life of imatinib is 18 hours. Additionally, literature and own data show a half-life of less than 16 hours in healthy subjects. In few subjects, the plasma concentrations are below quantification at 72.0 hours. Profiling over 48 hours is deemed sufficient as more than 80% of the total AUC is covered.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Please replace AUC72 by AUCt	