21 May 2015
EMA/CHMP/116444/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'draft tadalafil product-specific bioequivalence guidance' (CHMP/PKWP/EMA/423735/2013)

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
3	Teva Pharmaceuticals Ltd
4	Cipla Ltd.
5	Zentiva, k.s., Czech Republic (Jiri Hofmann)

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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.

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4	As per the guidance background, both fasting and fed bioequivalence studies are proposed for this product as “reference product is considered to have specific formulation characteristics to enhance the rate of absorption of the drug…” We are not in agreement to background for this guidance. As per Scientific Discussion available for Cialis Procedure No: EMEA/H/C/000436/X/26-27, it only contains conventionally used excipients, a micronized API and the manufacturing process by high shear granulation. There is no special formulation characteristic in the reference product. It is only a conventional tablet formulation. Hence a fasting BE study being the most sensitive to detect any potential differences between formulations should be sufficient in this case. This is also in line with the requirements of the Guideline on the investigation of bioequivalence wherein a fasting study is recommended where the SmPC recommends intake of the reference medicinal product on an empty stomach or irrespective of food intake.	If the generic is manufactured using the same technology and similar formulas as the originator it may be justifiable to deviate from the guidance by avoiding the fed study.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
15	1	**Comment:** We do not agree with line 15 of the draft guideline on tadalafil: "The reference product is considered to have **specific formulation characteristics** to enhance the rate of absorption of the drug". **Our arguments:** 1) Cialis® is an **immediate release** (IR) product. 2) **Formulation**: no special ingredients, matrix formation or solubility enhancers, except for the commonly used wetting agent – sodium lauryl sulfate (SLS). The originator company declared all Cialis®'s excipients are conventional, as stated in the EPAR: *"**Conventional pharmaceutical excipients** lactose monohydrate, hydroxypropylcellulose, sodium laurilsulfate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate (vegetable origin), hypromellose, triacetin, titanium dioxide (E171), iron oxide (E172), and talc are of Ph. Eur/USP/JP quality."* The originator company also detailed the function of each of the formulation components, and none of them have special or unusual functions: *"Excipients used for the 2.5 and 5 mg tablets are identical to those used for the approved tablets: combination of lactose monohydrate and spray dried lactose monohydrate to promote a rapid dissolution; hydroxypropylcellulose (binder); croscarmellose sodium (disintegration agent), laurisulfate (wetting agent) and magnesium stearate (lubricant)."* 3) **Process**: according to the originator company declaration, the manufacturing process is wet granulation, wet sizing, drying, dry sizing, blending,	If the generic is manufactured using the same technology and similar formulas as the originator it may be justifiable to deviate from the guidance by avoiding the fed study.

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		compression and coating, which are common practices in the art. "*The process for the manufacturing of the finished product follows* ***conventional pharmaceutical practices****, which includes aqueous wet granulation, sizing, and drying steps of tadalafil with hydrophilic excipients, followed by dry sizing of the granulate and then blending with additional excipients. The final blend is compressed into tablets, which are subsequently coated.*" [Cialis® EPAR] Moreover, according to US patent 7,182,958 B1 the Brand presents 13 examples for different formulations, all of them manufactured by simple wet granulation process, followed by wet milling, drying, dry milling compression and coating. In addition, this patent mentions coprecipitation of β-carboline with polymer as a method to enhance this poor soluble drug bioavailability and added that this method is "less than ideal for pharmaceutical formulations" (p1, Line 52). The reasons are the difficulties to generate reproducible product, and the too long t_{max} achieved. (See Citation 1 from patent US 7,182,958 B1, below). Thus, it can be concluded from this patent that Cialis® is not manufactured by special nonconventional methods, such as co-precipitation. 4) **API micronization**: According to Cialis EPAR, the Brand uses micronized API to enhance the tablet's dissolution: "*Studies carried out on the active substance showed that: thermodynamically stable, crystalline, nonhygroscopic and* ***micronised*** *tadalafil is incorporated into a wet granulation to consistently produce tablets with good homogeneity and the desired dissolution characteristics.*" The Brand's US patent 6,821,975 B1 claims for an API in which 90% of its particles have a Particule Size Distribution (PSD) smaller than 40µm (claim 1) and even smaller than 10µm (claim 4). However, using micronized API is not considered to be "specific formulation characteristics". It is a	

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		common approach used for several drug substances in order to increase solubility and is therefore not comparable to the examples given in the guideline on the Investigation of Bioequivalence (I.e. microemulsions, solid dispersions). --- Citation 1 from patent US 7,182,958 B1 : The poor solubility of many β-carbolines useful as PDE5 inhibitors has prompted the development of coprecipitate preparations, as disclosed in Butler U.S. Pat. No. 5,985,326. Briefly described, coprecipitates of β-carbolines with a polymer, e.g., hydroxypropyl methylcellulose phthalate, were prepared, then milled, mixed with excipients, and compressed into tablets for oral administration. However, studies revealed some difficulties in generating precisely reproducible lots of coprecipitate product, thereby making the use of coprecipitates less than ideal for pharmaceutical formulations. In addition, clinical studies involving administration of tablets containing such a coprecipitate preliminarily revealed that maximum blood concentration of the β-carboline is achieved in 3 to 4 hours, with the average time for onset of a therapeutic effect as yet not precisely determined. When used for the treatment of sexual dysfunction, such as male erectile dysfunction or female arousal disorder, a more rapid attainment of maximum blood concentration, along with a greater prospect for rapid onset of therapeutic effect, is desired by patients, who prefer more immediate effects. **Proposed change (if any):** Only fasted state comparison of test to reference formulations is required. (see also next point)	

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15		**Comment:** We do not agree with line 15 “it cannot be assumed that the impact of food will be the same” and the implication that there is a need to perform both fasted and fed state comparisons of test to reference formulations. One rationale to request both studies would be the observation of large differences between fasted and fed administration in tadalafil products. For the reference product such large differences were not seen according to the below study retrieved from Cialis NDA 021368 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-368_Cialis_BioPharmr_p3.pdf In this study there is a very mild food effect, which is mainly attributed to Cmax (16% increase), leading, in this study, to a deviation from the conventional bioequivalence limits for confidence interval. There was no deviation from the conventional limits observed for AUC. This slight deviation in Cmax is not thought to have any significant clinical implications. This is the rationale for the originator company’s statement: "*The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food*." **Proposed change (if any):** Only fasted state comparison of test to reference formulations is required. (see also previous point)	If the generic is manufactured using the same technology and similar formulas as the originator it may be justifiable to deviate from the guidance by avoiding the fed study.

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Background of strength	2	**Comment:** In order to keep the consistency, “low solubility” should be added **Proposed change (if any):** Linear PK and low solubility in the dose range 2.5 mg – 20 mg	Accepted.
Line 15 BE study design: “The reference product is considered to have specific formulation characteristics to enhance the rate of absorption of the drug and therefore, it cannot be assumed that the impact of food will be the same regardless of formulation. The product can be taken	3	**Comment:** We do not agree with to “The reference product is considered to have specific formulation characteristics to enhance the rate of absorption of the drug”. **Our arguments:** 5) Cialis® is IR product. 6) Formulation: no special ingredients, matrix formation or solubility enhancers, except of common used wetting agent – SLS. The innovator declared all Cialis®'s excipients are conventional, as stated in EPAR: "**Conventional pharmaceutical excipients** lactose monohydrate, hydroxypropylcellulose, sodium laurilsulfate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate (vegetable origin), hypromellose, triacetin, titanium dioxide (E171), iron oxide (E172), and talc are of Ph. Eur/USP/JP quality." The brand also detailed the function of each of the formulation components, and none of them have special or unusual function: "Excipients used for the 2.5 and 5 mg tablets are identical to those used for the approved	If the generic is manufactured using the same technology and similar formulas as the originator it may be justifiable to deviate from the guidance by avoiding the fed study.

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without regard to food. Thus, both fasted and fed state comparisons of test to reference formulations are required."		tablets: combination of lactose monohydrate and spray dried lactose monohydrate to promote a rapid dissolution; hydroxypropylcellulose (binder); croscarmellose sodium (disintegration agent), laurisulfate (wetting agent) and magnesium stearate (lubricant). 7) Process: according to the innovator declaration, the manufacturing process is wet granulation, wet sizing, drying, dry sizing, blending, compression and coating, which are common practices in the art. "The process for the manufacturing of the finished product follows **conventional pharmaceutical practices**, which includes aqueous wet granulation, sizing, and drying steps of tadalafil with hydrophilic excipients, followed by dry sizing of the granulate and then blending with additional excipients. The final blend is compressed into tablets, which are subsequently coated." [Cialis® EPAR] Moreover, according to US patent 7,182,958 B1 the Brand presents 13 examples for different formulations, all of them manufactured by simple wet granulation process, followed by wet milling, drying, dry milling compression and coating. In addition, this patent mentions coprecipitation of β-carboline with polymer as a method to enhance this poor soluble drug bioavailability and added that this method is "less than ideal for pharmaceutical	

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		Citation 1 from patent US 7,182,958 B1 : The poor solubility of many β-carbolines useful as PDE5 inhibitors has prompted the development of coprecipitate preparations, as disclosed in Butler U.S. Pat. No. 5,985,326. Briefly described, coprecipitates of β-carbolines with a polymer, e.g., hydroxypropyl methylcellulose phthalate, were prepared, then milled, mixed with excipients, and compressed into tablets for oral administration. However, studies revealed some difficulties in generating precisely reproducible lots of coprecipitate product, thereby making the use of coprecipitates less than ideal for pharmaceutical formulations. In addition, clinical studies involving administration of tablets containing such a coprecipitate preliminarily revealed that maximum blood concentration of the β-carboline is achieved in 3 to 4 hours, with the average time for onset of a therapeutic effect as yet not precisely determined. When used for the treatment of sexual dysfunction, such as male erectile dysfunction or female arousal disorder, a more rapid attainment of maximum blood concentration, along with a greater prospect for rapid onset of therapeutic effect, is desired by patients, who prefer more immediate effects. **Proposed change (if any):** Only fasted state comparison of test to reference formulations is required. (see also next point)	
Line 15 BE study design: "The reference product is considered to have	3	**Comment:** We do not agree with the need to perform both fasted and fed state comparisons of test to reference formulations. One rationale to request both studies would be the observation of large differences between fasted and fed administration in tadalafil products.	If the generic is manufactured using the same technology and similar formulas as the originator it may be justifiable to deviate from the guidance by avoiding the fed study.

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specific formulation characteristics to enhance the rate of absorption of the drug and therefore, it cannot be assumed that the impact of food will be the same regardless of formulation. The product can be taken without regard to food. Thus, both fasted and fed state comparisons of test to reference formulations are required.		For the reference product such large differences were not seen according to the below study retrieved from Cialis NDA 021368 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-368_Cialis_BioPharmr_p3.pdf In this study there is a very mild food effect, which is mainly attributed to Cmax (16% increase), leading, in this study, to a deviation from the conventional limits of confidence interval. There was no deviation from the conventional limits observed for AUC. This slight deviation in Cmax is not thought to have any significant clinical implications. This is the rationale for the Brand's statement: "*The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food*." **Proposed change (if any):** Only fasted state comparison of test to reference formulations is required. (see also previous point)	
Line(s) 15 to 16 (Table)	5	**Comment:** As per the reference SmPC, tadalafil tablet may be taken with or without food. An open-label, two-period	If the generic is manufactured using the same technology and similar formulas as the originator it may be justifiable to deviate from the guidance by avoiding the fed study.

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		cross-over study conducted in healthy volunteers showed that the rate and extent of absorption of tadalafil were not significantly influenced by presence of high fat, high calorie meal (FDA, NDA 21-368). The 20 mg market image tablet used in this study was identical to the proposed commercial tablet. In addition, in pivotal phase III clinical trials where tadalafil proved to be superior over placebo, the dosing instructions were non-specific and tadalafil tablet could be taken without regard to food (Cialis, EMEA/H/C/000436, EPAR Scientific Discussion). These findings demonstrate that the reference product does not have the specific formulation characteristics claimed in the Background information of draft specific guidance. Finally, for products where the SmPC recommends intake of the reference medicinal product irrespective of food intake, the bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect potential difference between formulations (EMA Guideline on Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1/Corr). In conclusion, tadalafil bioequivalence study should be performed only under fasting conditions. **Proposed change**: Table 'Requirements for bioequivalence demonstration (PKWP)': Section BE study, in the recommendation regarding posology modify to: (1) ☒ fasting, ☐ fed, ☐either fasting or fed, and (2) delete the Background	

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		information. In the section Number of studies, modify to: one single dose study.	