21 May 2015
EMA/CHMP/116324/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'draft capecitabine product-specific bioequivalence guidance' (CHMP/PKWP/EMA/423732/2013)

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	Absorption Systems
3	MEB, The Netherlands
4	Alkem Laboratories Limited
5	SciencePharma (Poland)
6	BEBAC – Consultancy Services for Bioequivalence and Bioavailability Studies

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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	The BCS classification of capecitabine should be denoted as “BCS I”, rather than “neither of the two” in the product-specific bioequivalence guidance. BCS classification is based on two properties of the active pharmaceutical ingredient (API), namely solubility and permeability (*in vitro*)/absorption (*in vivo*), and one property of the formulated drug product, namely dissolution. Several literature references, reviewed by Reigner et al. [1], report complete recovery of the parent compound and urinary metabolites in clinical pharmacokinetic and mass balance studies. The FDA prescribing information for Xeloda® (capecitabine) [2] reports that 95.5% of the administered dose is recovered in urine and 2.6% in feces, for a total recovery of 98.1%; the data are from a clinical study with [^{14}C]-capecitabine conducted by Judson et al. [3]. Obviously, complete recovery of the parent compound and metabolites is secondary to complete absorption; thus, the clinical data support a designation of capecitabine as well absorbed,	Absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine.

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	according to either the EMA (≥ 85%) or FDA (≥ 90%). Therefore, based on regulatory reviewed *in vivo* absorption data, capecitabine should be classified as Class I according to BCS criteria. Additionally, *in vitro* test system(s) are capable of designating capecitabine as BCS highly permeable because of its clinical dose proportionality; i.e., systemic exposure (AUC) and/or C_{max} increasing in proportion to the dose in a multiple-dose clinical pharmacokinetic study. Two studies have established dose proportionality for the parent compound and the primary metabolite, one up to a dose of 829 mg/m^2 [4] (1492 mg based on an average surface area of 1.8 m^2 [5]) and the second up to a dose of 1757 mg/m^2 [6] (3163 mg). The implication is that clinical exposure to capecitabine is neither dependent on active uptake nor limited by active efflux and that the drug substance is primarily absorbed through passive transport mechanisms along the intestinal tract. Furthermore, limiting the basis of the capecitabine BCS classification to the corresponding summary documents will unduly constrain applicants in terms of eligibility for BCS-based biowaivers. To expand the application of the BCS biowaiver, we suggest that the product-specific recommendation for capecitabine also incorporate the recommendations of other regulatory bodies with regard to biowaiver applicability. Specifically, the USFDA explicitly recommends the BCS biowaiver option for capecitabine in the product's individual recommendation [7]. Highlighting eligibility for BCS biowaivers in the product-specific recommendations is an excellent mechanism for promoting this science-based approach and minimizing unnecessary clinical testing, particularly for highly variable drugs (HVDs) and drugs with potential for side-effects, like capecitabine. Regarding the general verbiage for "BCS Classification" in the	

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	product-specific recommendations, the language “neither of the two” implies that a compound has been definitively classified as neither BCS I nor BCS III. Such language discourages applicants from considering the BCS biowaiver route and could potentially make generic development more expensive and circuitous for certain products. If a compound has not definitively been classified as BCS I (based on clinical and or *in vitro* data), then the BCS Class should be marked as “to be determined” and the agency should consider providing insights on which type of data need to be generated (e.g. permeability and/or dose relevant solubility) to review drug substance eligibility for a BCS based biowaiver. This is more in line with the corresponding note (Line 17) which calls for the applicant to confirm the BCS classification at the time of submission. [1] Reigner B., Blesch K., and Weidekamm E., Clinical pharmacokinetics of capecitabine. Clin. Pharmacokinet. 2001;40(2):85-104. [2] Xeloda® (capecitabine) prescribing information, Genentech USA, Inc., revised 2/2011: http://www.gene.com/gene/products/information/xeloda/pdf/pi.pdf. [3] Judson I.R., Beale P.J., Trigo J.M., Aherne W., Crompton T., Jones D., Bush E., and Reigner B., A human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of ^{14}C-labelled drug. Invest. New Drugs. 1999;17(1):49-56. [4] Mackean M., Planting A., Twelves C., Schellens J., Allman D., Osterwalder B., Reigner B., Griffin T., Kaye S., and Verweij J., Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J. Clin. Oncol. 1998 Sep;16(9):2977-2985 [5] International Commission on Radiological Protection No. 23, Report of the Task Group on Reference Man, Pergamon Press, 1975.	

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	[6] Budman D.R., Meropol N.J., Reigner B., Creaven P.J., Lichtman S.M., Berghorn E., Behr J., Gordon R.J., Osterwalder B., and Griffin T., Preliminary studies of a novel oral fluorpyrimidine carbamate: capecitabine. J. Clin. Oncol. 1998 May;16(5):1795-1802. [7] FDA Draft Guidance on Capecitabine: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm083276.pdf	
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 under the same conditions.	1. Accepted. The template has been modified. Of note, even in the case of principle eligibility of a certain drug substance, the BCS based biowaiver may be impossible to be applied because requirements in terms of excipients and/or in vitro dissolution /Tvs R) are not achievable. Then, an in vivo study will be necessary. 2. The comment has been acknowledged; however, this is addressed in the guideline, therefore no further action is needed. 3. Accepted. 4. Text has been changed to: absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine.
4	Based on the available literature evidence Capecitabine is freely soluble in methanol, soluble in acetonitrile and in alcohol, sparingly soluble in water, After oral administration, capecitabine is rapidly and extensively absorbed unchanged from the GIT tract. Capecitabine reached peak blood levels in about 1.5 hours (T_{max}) which indicate	Absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine.

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	high permeability of the molecule. USFDA Draft guidance on Capecitabine has suggested BCS waiver option based on the appropriate documentation regarding high solubility, high permeability and rapid dissolution. Therefore we request agency to consider the option for BCS based waiver if company provide appropriate documentation regarding solubility, permeability and dissolution.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	1	**Comment:** BCS classification The draft guideline states that “Capecitabine is an unstable compound in acidic medium. The available data on solubility does not allow its BCS classification.” However, the instability is only observed at pH 1 but at pH 2, which is still acidic condition, the required stability is given. According to the posology recommendations in the product information, Capecitabine tablets are to be taken orally 30 min after food intake. Since stomach pH increases to pH ranges of 3-5 after food intake, the stability in strong acidic conditions (pH 1) is not physiologically relevant for Capecitabine tablets. In addition, BCS classification should be confirmed by the applicant with own data (i.e. solubility of API manufactured by the applied active substance manufacturer). Furthermore, the draft FDA product specific guideline1 for capecitabine indicates it is considered a BCS Class I drug. We therefore believe that the possibility for biowaiver should be reflected in the final EMA guideline provided the high solubility is evidenced (even in low pH). 1 http://www.fda.gov/downloads/Drugs/GuidanceCompli	The comment is acknowledged. However, the specific prerequisites to apply the BCS-based biowaiver (which is already a very simplified approach to prove bioequivalence) should be fully met. Hence, the current wording for capecitabine considers that accordingly: “Absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine.”

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		anceRegulatoryInformation/Guidances/ucm083276.pdf “Recommended studies: 2 Options: BCS waiver or In-Vivo Study I. BCS Waiver option: It may be possible to request a waiver of in-vivo testing of this product provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence for Immediate – Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System is submitted in the application. You may use the information contained in the approved labeling of the reference product. Peer reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon review of the data submitted in the application.” **Proposed change (if any):** Remove BCS class checkbox and replace it by following comment (already stated as footnote in lines 17 and 18) “The BCS classification should be confirmed by the applicant at time of submission based on available data (solubility experiments, literature, etc.). Solubility tests (and dissolution tests when applying for BCS waiver) should be performed within the	

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		physiological relevant pH range 2 to 6.8."	
	1	**Comment:** High Variability The high variability of Cmax for capecitabine is well known and documented. As such we believe it cannot be categorised as 'critical dose drug' or narrow therapeutic index drug as preferred EU terminology. **Proposed change (if any):** 'Widening of the usual acceptance criteria for Cmax is not accepted because capecitabine is considered a "critical dose" highly variable drug. '	Accepted and supported by the EMA Oncology Working Party.
	1	**Comment:** 'Critical dose drug' is a term that is not referenced in the main EU guideline on bioequivalence for immediate release products. As such it is important that it is clearly defined so that interpretation is harmonised. **Proposed change (if any):** Please add a paragraph or a glossary to introduce a definition for 'critical dose drug'.	The comment has been acknowledged and addressed in the final version of the guideline.
	1	**Comment:** Fast versus fed study In the case an applicant chooses to conduct a PK study, the draft guideline recommends that a fed study is carried out to minimise the risk of vomiting. Given the indication of the molecule, the PK study will be done on patients. It is important that the final guideline provides the	The comment has been acknowledged. Any deviation from the product specific guidelines, if scientifically justified, could be acceptable.

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		option to use regular, non-high fat meal in the fed study because it may be difficult to have cancer patients complete a high fat meal before dosing. **Proposed change (if any):** When conducting a PK study in patients, a regular, non-high fat meal is acceptable for the fed study.	
	1	**Comment:** BCS class II or IV (line 18) The draft guideline states that no further solubility investigations are needed if a drug substance has been classified as BCS class II or IV. However the BCS classification depends on the highest single dose and should therefore be determined by the applicant considering the applied drug product (posology/indication of own product) **Proposed change (if any):** Remove sentence stated in line 18 and keep sentence in line 17 only.	Accepted.
Line 15: "BCS Class… Neither of the two"	2	**Comment:** Based on published clinical data, capecitabine does exhibit complete absorption (≥ 85%) and may be classified as BCS I according to the EMA standards. Thus, its solubility at pharmaceutically relevant pH values and stability at acidic pH (combined with rapid absorption, resulting in a T_{max} of ~1.5 hr) are sufficient to enable complete absorption. In addition, the USFDA recognizes that this compound is eligible for BCS biowaiver in the corresponding individual product	The comment is acknowledged. However, the specific prerequisites to apply the BCS-based biowaiver (which is already a very simplified approach to prove bioequivalence) should be fully met. The compound is reported to be unstable at pH 1. Hence, the US-FDA proposal is not followed and the current wording for capecitabine considers that accordingly: "Absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine."

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		recommendation. **Proposed change (if any):** BCS Class of capecitabine should be marked as “BCS I” instead of “neither of the two”. For other compounds, which have not definitively been classified as BCS I, the verbiage should be changed from “neither of the two” to “to be determined”. This is more in line with the corresponding note (Line 17) which calls for the applicant to confirm the BCS classification at the time of submission. The language “neither of the two” implies that a compound has been definitively classified as neither BCS I nor BCS III. Such language may discourage applicants from further investigating the BCS biowaiver route.	
Line 15: “The available data on solubility does not allow its BCS classification .”	2	**Comment:** Verbiage implies that BCS solubility classification of capecitabine is not achievable. The nature of this statement may discourage applicants from further investigating the BCS classification of capecitabine. Language is also inconsistent with recommendations for other compounds for which BCS Class is marked as“neither of the two”. For example, the product-specific recommendation for oseltamivir explicitly states that “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”. **Proposed change (if any):** Language should be	The comment is acknowledged. However, in the case of capecitabine is not considered a matter of wording. The specific prerequisites to apply the BCS-based biowaiver (which is already a very simplified approach to prove bioequivalence) should be fully met. The compound is reported to be unstable at pH 1. Hence, the current wording for capecitabine considers that accordingly: “Absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine.”

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		more consistent with similar recommendations, such as that for oseltamivir. A statement should be added that "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".	
Line 16: "...this guidance is not applicable to highly variable drugs"	2	**Comment:** The "highly variable" nature of any drug, including capecitabine, should not restrict a potential BCS biowaiver. In fact, biowaivers are particularly valuable for highly variable drugs (HVDs) because these drugs exhibit consistently inconsistent PK due to extensive first-pass metabolism. As a result, human mass balance and bioavailability studies may result in ambiguous or incorrect BCS classification because the variability inherent in human PK studies is compounded by the intrinsic properties of the drug substance. In such cases, *in vitro* testing provides more direct, consistent, and accurate classification of absorption, as the variability associated with permeability and solubility measurements is less dependent on the factors that exaggerate the variability of human testing. Well-validated *in vitro* models that are representative of intestinal absorption provide a reliable alternative for pivotal BCS classification. **Proposed change (if any):** Remove line 16 from the product-specific guidance, or state that BCS based biowaiver is applicable to highly variable drugs.	In general, it is fully agreed that the "highly variable" nature of any drug will not restrict a potential BCS-based biowaiver. However, in the case of capecitabine this is not the reason but limitations on stability at acidic pH. Hence, the wording is as follows: "Absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility do not allow the BCS classification of capecitabine."
Study	3	**Comment:**	Accepted.

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design: Patients		Patients because of the inhibition of DNA synthesis **Proposed change (if any):**	
"Bioequivalence assessment" line in the table	5	**Comment:** It is stated in the Guidance that widening of the usual acceptance criteria for Cmax is not accepted because capecitabine is considered a "critical dose" drug. It should be noted that there is a discussion among scientists that capecitabine should in fact be considered as "non-critical dose drug" (Gieschke 2003). The reason for the possibility of widening the 90% confidence interval for the ratio of geometric least squares means for ln-transformed pharmacokinetic parameter C_{max} is based on the relevant published data on capecitabine. It is stated that "safety in humans does not correlate with C_{max} values". Furthermore, preclinical experiments in mice have shown that the antitumor activity is similar when the same daily dose of capecitabine is administered once or twice daily. Assuming dose-proportional pharmacokinetics in mice, the once-daily dosing would have produced a Cmax twice as high as the twice-daily dosing regimen with the same AUC. Therefore, this suggests that AUC and not C_{max} correlates with antitumor activity in mice (Cassidy 1999). *In vitro* studies investigating the cell killing effect of 5-FU have shown that 5-FU is an 'AUC-dependent drug', that is, short exposure requires high concentrations to obtain the cell killing effects whereas the same effect can be obtained with longer exposure	Accepted.

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		to lower concentrations (Inaba 1990). Generally, in the clinical use of cytotoxic agents, efficacy and safety correlates better with AUC rather than with C_{max}". In a clinical study investigating food effect on pharmacokinetics of capecitabine and its metabolites following administration in cancer patients it is stated that the most important pharmacokinetic parameter to predict safety and efficacy is AUC, not C_{max}, apart from that capecitabine itself is inactive (not cytotoxic) drug (Reigner 1998, Cassidy 1999). Moreover, results of clinical study conducted to assess the relationship between systemic exposure to capecitabine metabolites and parameters of efficacy and safety in patients from 2 phase III studies allowed to lead to a conclusion that therapeutic monitoring for capecitabine dose adjustment has no value (Gieschke 2003). Moreover, capecitabine is a high-variability drug taking into consideration C_{max}, however, the variability is an internal property of the active substance, which can be seen in e.g., Assessment Reports of generic drugs published by EMA. This implicates very high numbers of patients involved in bioequivalence (BE) studies, especially when widening of acceptance criteria is not allowed. However, the number of patients is artificially overestimated in such situation as it is known that the higher number of patients the confidence intervals are narrower. This is the case why the results of conducted BE studies were positive and generic companies	

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		registered their medicinal products. In our opinion such approach that lead to artificially higher number of patients involved in a BE study should not be recommended from ethical point of view. In case medicinal products turn out not to be bioequivalent (too low AUC – will results in ineffective treatment, too high AUC – in higher risk of adverse effects) then the excessive number of patients will be unnecessary exposed to investigational medicinal products . **Proposed change:** Widening of the usual acceptance criteria for Cmax is acceptable if appropriately justified based on the results of intra-subject variability for the reference product observed in a semi-replicate or full-replicate study.	
Line 15	6	**Comment on:** “Strength: 500 mg because it is the highest strength” “Number of studies: one single dose study” Make clear that the study’s design must follow the recommended posology. The standard treatment scheme for metastatic breast or colorectal cancer patients is 2,500 mg/m²/day in two divided doses for two weeks followed by a one week treatment-free interval (*e.g.*, for a patient with a 2 m² body surface area a *single dose* is 5×500 mg). However, *two* doses / day should be administered. We consider a single dose study (*i.e.*, interrupting the treatment) unethical.	It is acceptable for the daily dose to be divided in two. Furthermore, higher doses can be applied if needed for patients.

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		Proposed change (if any): State unambiguously the treatment scheme, not only the strength.	