26 April 2023
EMA/CHMP/735541/2022
Committee for Medicines for Human Use (CHMP)

Overview of comments received on 'Ibuprofen oral use immediate release formulations 200–800 mg product-specific bioequivalence guidance' (EMA/CHMP/356876/2017 Rev.1)

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

Stakeholder no.	Name of organisation or individual
1	AESGP
2	Angelini Pharma S.p.A
3	BEBAC; Institute of Medical Statistics, University of Vienna, Austria
4	Catalent Pharma Solutions
5	Cliantha Research
6	Krka, d. d., Novo mesto
7	Medicines for Europe
8	Reckitt

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We do not believe that the new criteria of Comparable median (≤ 20% difference) for T_{max} is based on scientific data demonstrating that such a change in median T_{max} between reference and test product will lead to any clinically meaningful change. Additionally, because of the inherent variability of T_{max} for API such as Ibuprofen we believe that the proposed criteria is too restrictive and would hinder studies sponsors by making it extremely difficult to design a suitable bioequivalence study and demonstrate bioequivalence between product. Finally, we are concerned on the potential impact to current pk study design, specifically increased demand on patient numbers and blood draws from a feasible and ethical concern. In the absence of scientific rational, we oppose a T_{max} of 20%. We would like first of all to understand the reasons for proposing a T_{max} in the first place; we would be open to consider and discuss a proposed T_{max} which is scientifically grounded and justified based on efficacy and safety considerations. You mention 'Comparable median (≤ 20% difference) and range for T_{max}'. Showing a relative or percentage difference would imply a statistical approach based on ratios. In theory T_{max} is a continuous variable, but practically it is not, as the timepoints are pre-defined. Therefore, assumptions on the distribution for a statistical approach based on ratios are not fulfilled. A possibility may be to apply a non-parametrical approach on differences and compare these results on a numerical manner with the point estimates (eg	**Not accepted.** A comparable median T_{max} is required for drugs where the onset of action is clinically relevant. Only the point estimates of T_{max} are compared according to the Guideline on the Investigation of Bioequivalence, whereas the demonstration of bioequivalence for the non-parametric 90% CI of T_{max} was required in the past. The revision of the PSBGL intends to clarify the regulatory expectations by defining an objective criterion to avoid arbitrations. It is considered necessary to define what is considered a comparable T_{max}. Note that the requirements for the comparison of the rate of absorption for drugs where the onset of action is clinically relevant are being harmonised in ICH M13. There are several studies showing that T_{max} differences of this magnitude are observed between ibuprofen acid and ibuprofen salts (lysine, arginine or sodium) and it is known that these products differ in onset of action. - Black P, Max MB, Desjardins P, Norwood T, Ardia A, Pallotta T. 2002. A randomized, double-blind, placebo-controlled comparison of the analgesic efficacy, onset of action, and tolerability of ibuprofen arginate and ibuprofen in postoperative dental pain. Clin Ther 24(7):1072–1089. - Mehlisch DR, Ardia A, Pallotta T. 2002. A controlled comparative study of ibuprofen arginate versus conventional ibuprofen in the treatment of postoperative dental pain. J Clin Pharmacol 42(8):904–911.

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	median) and we would be keen to discuss this as part of the scientific discussion we would wish to have further to the sending of comments.	- Mehlisch DR, Ardia A, Pallotta T. 2003. Analgesia with ibuprofen arginate versus conventional ibuprofen for patients with dysmenorrhea: A crossover trial. Curr Ther Res Clin Exp 64(6):327–337. In the current proposal, only the point estimates of T_{max} are compared, whereas the demonstration of bioequivalence for the non-parametric 90% CI of T_{max} was required in the past. Similarly, for drugs where the onset of action is clinically relevant, other jurisdictions require the demonstration of equivalence based on the 90% CI of partial AUCs, which is also more demanding in sample size than this comparison of medians. Therefore, it is agreed that more sampling times are needed to characterise more accurately T_{max}, but the present approach is the less demanding approach amongst those available. The present approach is not based on ratios. The present approach is the following: If the reference median T_{max} is at 1.5 h, 20% of 90 minutes is 18 minutes. Therefore, if the test product has a median of 1.75 h (i.e. 105 minutes), the difference of 15 minutes is acceptable.
3	The clarification what is "meant by 'comparable' T_{max}" is appreciated.	**Accepted.** Comparable is defined by the acceptance range, i.e. differences ≤ 20% (and more precisely specified within 80–125%) of the value of the reference median.
4	From a patient centred rationale, there will be no effect on patient safety through the introduction of the additional requirement for T_{max} comparability, however, drug product development and innovation providing the patient with more choice and convenient	**Not accepted.**

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	delivery platforms will be severely restricted by the introduction of the requirement for the current proposed T_{max} similarity. Furthermore, a slower T_{max} will have no effect on patient safety, it can be demonstrated as per the current prescribed dosing strategy (1 or 2, 200mg doses 3 times a day) that even if the T_{max} would be delayed, carry over would not lead to a level of Ibuprofen that can cause a risk to the patient. There are several aspects supporting the relative patient safety, including: **The excretion path**. The half-life for the elimination of Ibuprofen is relatively short, ranging from 0.9 to 2.5 hours with a mean of 1.9 hours (1). Excretion of the metabolites in the urine is usually complete within 24 hours of taking the last dose and the total urinary excretion of Ibuprofen and its metabolites is a linear function of dosage (3). The rapid metabolism and excretion of Ibuprofen explains, to some extent, the relatively low toxicity of Ibuprofen compared with some other NSAIDs. It has been shown that the reported reduction in glomerular filtration associated with NSAIDs is related to their half-life (2). **Daily dose of Ibuprofen.** Ibuprofen, at doses of 1200 mg or below, acts predominantly as an analgesic and antipyretic, although it still exhibits some anti-inflammatory properties (4). This represents a therapeutic advantage, as many types of acute and recurrent pain syndromes have an inflammatory component. A major advantage of Ibuprofen over other common OTC analgesics e.g., paracetamol, is that it has a wide therapeutic window and hence is comparatively safe in overdose (4). A systematic review (1980-2009) of published and unpublished data was carried out to identify studies which contain adequate documentation to enable	It is agreed that the safety is not addressed by T_{max}, but the onset of action is relevant for the efficacy of an analgesic product where timely onset of action is desirable. The demonstration of comparable T_{max} is necessary for generics of ibuprofen. The development of innovative dosage forms and methods of administration that are intended to offer the patient more options to choose and convenient methods of administration should address the impact of the T_{max} on the onset of action. These alternatives are not restricted, but patients should be informed not only about the advantages of the new dosage forms and methods of administration (e.g. possible intake without water), but also about how they impact on the onset of action (delayed onset of action if taken without water). As this requirement is based on medians without taking into account the non-parametric 90% confidence interval, it is not agreed that larger BE clinical studies are necessary to ensure that a statistical evaluation can be performed. The proposed comparison can be conducted with any sample size. The proposed change is not acceptable because T_{max} is a primary PK parameter for drugs where the onset of action is clinically relevant. It is not accepted that T_{max} can be removed from the list of primary PK parameters. With the current guideline text: "comparable median T_{max} and its variability between test and reference product" was not sufficiently clear how to evaluate comparable median T_{max} values. The objective

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	an assessment of safety of Ibuprofen at OTC doses (up to maximum 1200mg /day). (5) **High-dose ibuprofen.** In patients with cystic fibrosis, high-dose Ibuprofen has been proposed as a possible treatment (6). Patients have been treated with doses deliberately designed to achieve peak plasma concentrations between 50 and 100 µg/mL, in order to slow the progression of disease. These high concentrations were generally well tolerated by the patients, with no serious AEs noted (6,7). These concentrations of Ibuprofen are much higher than those observed in normal OTC posology dosing and have shown no risk to patients with the administered doses. New product introduction and innovation will be significantly more complex due to the high T_{max} intra-product variability observed for a range of Ibuprofen products and will need to meet a very narrow window of BE acceptance. Currently there are no modelling tools predicting the effect of product optimisation on the T_{max} to meet such tight requirements, which will lead to the requirement of more pilot clinical studies leading to larger BE clinical studies to ensure that a statistical evaluation can be performed (contradicting the requirement for statistical analysis). References: 1. Insel PA. Ibuprofen. In "Goodman & Gilman's The pharmacological basis of therapeutics". New York: NcGraw Hill; 1996. 2. Brater DC. Renal safety of ibuprofen: Pharmocokinetics aspects. International Conference on inflammapharmacology, Vth Symposium, 17-19 March 1997	of this revision is to clarify what is meant with comparable median T_{max}.

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	3. Davies NM. Clinical Pharmacokinetics of Ibuprofen, the first 30 years. Clin Pharmacokinet. 1998; 34: 101-114 4. Gulmez SE, Lassalle R, Jove J, Caridade G, Grolleau A, et al. Risk of hospital admission for liver injury in users of NSAIDs and non-overdose paracetamol (EPIHAM). Clin Therapeutics. 2015; Suppl 1: 37.8: e15. 5. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacol 2009; 17:275-342 6. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. N Engl J Med. 1995;332:848-54. 7. Lands LC, Milner R, Cantin AM, Manson D, Corey M. High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. J Pediatr. 2007;151:249-54. **Proposed change:** T_{max} to be removed from the 'Main Pharmacokinetic Variables' within the newly proposed guidance but to remain part of the 'Bioequivalence assessment' as 'comparable median and Range for T_{max}'. Include an assessment as per general BE guidance detailed on p 15/27, 4.1.8 *"if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median T_{max} and its variability between test and reference product*".	
7	The specific comments to ibuprofen draft product-specific bioequivalence guidance (EMA/CHMP/356876/2017 Rev.1*) provided below were also submitted to paracetamol (EMA/CHMP/356877/2022 Rev.1*) and tadalafil	**Partly accepted.** It is agreed that this change applies to these three drugs where the onset of action is considered clinically relevant.

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	(EMA/CHMP/315234/2014 Rev.2*) draft product-specific guidance(s) since all revisions concern the definition what is meant by 'comparable' T_{max} as an additional main pharmacokinetic variable in the bioequivalence assessment section of the guidance.	It is not an additional main PK variable since it was already a primary PK parameter for these three products. Now the criteria on how to assess the T_{max} differences have been defined in an objective manner.
7	The new proposal for acceptance criteria for median of T_{max} was introduced based on disagreement in registration procedure (IE/H/1132/001/DC) that involved ibuprofen formulations. In particular, referral for the Art. 10(1) application for an oral lyophilisate containing ibuprofen was triggered as it was considered by the objecting CMS that the bioequivalence requirements for T_{max} are not in line with the product-specific bioequivalence guideline (PSBGL) issued by PKWP. PKWP has been consulted during the referral procedure and confirmed that the presented T_{max} values are not to be considered "comparable", as mentioned in the PSBGL (CMDh minutes for the meeting on December 14 – 16, 2021, EMA/CMDh/89802/2022). Since this particular case represents a precedent for definition of general criteria, members of Medicines for Europe would appreciate if concrete data were made public. This would definitely contribute to transparency behind proposing a new criterion. Alternatively, example data sets of, in the PKWP point of view, comparable and non-comparable difference could be released, in order to permit stakeholder's review and further scientific discussion that must precede implementation of any new criteria affecting future submissions. These data shall include individual subject $T_{max(es)}$ along with additional relevant information (e.g., period and sequence information in case of cross-over design).	**Partly accepted.** It is not considered necessary to make public further data. Transparency on the criteria and how to apply them is given above in response to the first comment. Furthermore, it is not considered necessary to include individual subject $T_{max(es)}$ along with additional relevant information (e.g. period and sequence information in case of cross-over design) because the analysis is based on the medians of test and reference in a straightforward numerical subtraction.

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8	According to the "Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr**, the evaluation of T_{max} should be performed when the rapid release of the substance is clinically relevant and of importance for the onset of action or is related to adverse events (AE). Ibuprofen, a standard pain killer, not used in lifesaving events does not meet the criteria that requires T_{max} to be evaluated. Furthermore, there is no data of any adverse events related to the rapid release of Ibuprofen from the formulation, meaning the inclusion of T_{max} in primary endpoint analysis is not justified. If statistical evaluation of T_{max} is not required then it is recommended the abovementioned guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr** is kept as is.	**Not accepted.** Even if not life-threatening, patients with pain (e.g. a simple headache) deserve to obtain pain relief with the test as soon as with the reference. The opinion expressed that ibuprofen as a standard pain killer does not meet the criteria that require T_{max} to be evaluated is not agreed. As stated above, this criterion is not related to safety.
8	The rationale behind the development of product-specific bioequivalence guidance, according to the Concept paper on the development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013), is to "facilitate transparent, predictable and scientifically robust assessment in future marketing authorisation procedures" and "to enable a consistent approach to the assessment of applications based on bioequivalence data, particularly generic applications, across all submission routes. However as the vast majority of NSAID and other painkiller APIs do not (yet) have product specific bioequivalence guidelines (with the exception of ibuprofen and paracetamol), the proposed additional requirement/restriction for these two APIs does not seem to allow for a consistent approach to be taken across similar APIs, particularly within the NSAID family e.g. diclofenac, dexibuprofen,	**Not accepted.** The clarification was needed because the criteria on how to decide if median T_{max} was comparable was not clear. Therefore, the purpose of this modification is to facilitate transparent, predictable and scientifically robust assessment in future marketing authorisation procedures and to enable a consistent approach to the assessment of applications based on bioequivalence data, particularly generic applications. Even for those NSAIDs for which a PSBGL has not been issued, it can therefore be implied that the same requirements are applied in the assessment of applications if they are used for acute pain relief. The final comment on the non-life-threatening condition has been addressed in the previous comment.

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	naproxen do not have product-specific bioequivalence guidelines which could result in less scrutiny for products containing these APIs vs ibuprofen, rather than the assessment of the product and its merits in the context of the specific application. Product specific bioequivalence guidelines are available for only a limited number of active ingredients, predominantly focusing on prescription drugs for serious conditions such as cancer drugs (Abiraterone, Alectinib, Cabozantinib, Capecitabine, Vismodegib, Sirolimus, Sunitinib, Lapatinib), anti-coagulants (Acenocoumarol, Apixaban), antidepressants (Agomelatine), blood pressure drugs (Aliskiren), antipsychotics (Asenapine, Paliperidone), epilepsy drugs (Zonisamide), and antibiotics (Telithromycin). According to the "Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr**, the evaluation of T_{max} should be performed when the rapid release of the substance is clinically relevant and of importance for the onset of action or is related to adverse events (AE). Ibuprofen, a standard pain killer, not used in lifesaving events does not meet the criteria that requires T_{max} to be evaluated. Furthermore, there is no data of any adverse events related to the rapid release of Ibuprofen from the formulation. If statistical evaluation of T_{max} is not required, then it is recommended the abovementioned guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr** is kept as it is.	

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	Proposed change: We believe the previous requirement was adequate as it allows for the context of the application to be taken into account and propose that remains in force.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	1	**Comments:** We believe the addition of a specific ≤ 20% difference parameter for T_{max} is not warranted at this time, as it has not been demonstrated in the scientific literature that differences above 20% - for any and all applications for ibuprofen – would have clinically relevant effects. We note that the 20% has been applied across all three updated guidelines out for consultation but it is reasonable to expect that a newly set criteria should stem from the grounds of undisputed scientific evidence. According to our literature searches we believe the proposal of 20% is not supported by clinical data. There is currently several existing PKPD model available in the literatures.[1,2,3] For example, using an antipyretic PKPD model, Troconiz et. al (2000), found that maximum antipyretic effect was similar and occurred at the same time for two formulations of Ibuprofen with a 1 hour difference in T_{max} (i.e., a 50% difference).[1] Another study using pain PKPD model by Cristofoletti and Dressman in 2014, showed that a 2.2 hour delay in T_{max} only translates into a 30 mins delay in the onset of dental pain relief and no difference in maximum efficacy.[2] The clear interpretation of findings from these two studies is that, even in the case where the T_{max} of Test and Reference products differ by significantly more than 20%, this difference would not be expected to have a significant impact on factors such as time to maximum antipyretic efficacy or time to onset	**Not accepted.** Even if the onset of action of the antipyretic effect was not sensitive to the T_{max} differences, onset of action of the analgesic effect is sensitive to differences in T_{max}. A 30-minute difference in this is considered clinically relevant. See response to the first comment above, where the small differences in T_{max} between the acid and the salts of ibuprofen have been detected as resulting in clinically relevant differences in the onset of action. - Black P, Max MB, Desjardins P, Norwood T, Ardia A, Pallotta T. 2002. A randomized, double-blind, placebo-controlled comparison of the analgesic efficacy, onset of action, and tolerability of ibuprofen arginate and ibuprofen in postoperative dental pain. Clin Ther 24(7):1072–1089. - Mehlisch DR, Ardia A, Pallotta T. 2002. A controlled comparative study of ibuprofen arginate versus conventional ibuprofen in the treatment of postoperative dental pain. J ClinPharmacol 42(8):904–911. - Mehlisch DR, Ardia A, Pallotta T. 2003. Analgesia with ibuprofen arginate versus conventional ibuprofen for patients with dysmenorrhea: A crossover trial. Curr Ther Res Clin Exp 64(6):327–337.

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		of analgesia as well as maximum efficacy. Therefore, we believe that the proposed criteria of ± 20% lacks clinical justification. *References:* *1- Trocóniz IF et al. Clinical pharmacokinetics. 2000 Jun;38(6):505-18.* *2- Cristofoletti R & Dressman JB. Journal of Pharmaceutical Sciences. 2014 Oct 1;103(10):3263-75.* *3- Li H et al. J Clin Pharmacol. 2012 Jan;52(1):89-101* **Proposed change:** In the absence of scientific rational, we oppose a T_{max} of 20%. We would like first of all to understand the reasons for proposing a T_{max} in the first place; we would be open to consider and discuss a proposed T_{max} which is scientifically grounded and justified based on efficacy and safety considerations.	
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	1	**Comments:** One of the stated aims of the product specific bioequivalence guidelines, according to the Concept paper on the development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013), is to aid studies sponsors by "facilitate(ing) the design of study programmes that meet the expectations of European Union regulators hence allowing for better predictability in terms of the assessment during the authorisation process".	**Not accepted.** See responses to previous comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		We believe the proposed criteria of comparable median (≤20% difference) will instead hinder studies sponsors by making it extremely difficult to design a suitable bioequivalence study, predict and demonstrate bioequivalence to meet the updated guideline, due to the inherent variability and "moving target" of the ≤ 20% difference parameter for T_{max}. This could result in multiple studies being required to find a "suitable" reference product, which meets the legal basis reference product requirements, and which then passes the ≤20% difference parameter for T_{max} – thus hindering rather than facilitating the design of study programmes and generic manufacturers would have more difficulties bringing more cost-effective products to market. Considering the faster formats of Ibuprofen, i.e., arginine, lysine, and sodium salts, a publication from Andrew Moore et al. (2014) reported an average T_{max} median for this faster format to be between 29–35 minutes.[1] The new guideline would require that the difference in T_{max} median for a newly developed test product of Ibuprofen arginine, lysine or sodium salt be less than 5.8-7 minutes in comparison to the reference. For standard Ibuprofen format the same publication from Moore reported an average T_{max} median of 90 minutes. Consequently, the new guideline would require that the difference in T_{max} median of a newly developed standard Ibuprofen and the reference be less than 18 minutes.	The suitable reference product for a generic application should not be based on a trial and error exercise. The reference product to which bioequivalence is to be demonstrated should be identified early in the development. For dosage forms and salt forms with a quicker T_{max}, sampling times may need to be taken every 5 minutes around the expected T_{max}, not only for a proper characterisation of T_{max}, but also for the proper characterisation of C_{max}. As few samples before C_{max} and several samples around C_{max} are needed, if T_{max} is expected 30 minutes after administration, sampling should be at e.g. 10, 20, 25, 30, 35, 40, etc., which would allow to conclude that the difference is less than 5 minutes if the T_{max} is observed in the same or an adjacent sampling time. Samples as early as 5 or 10 minutes after dosing are not infrequent. Regarding the comment on ibuprofen acid, with a median T_{max} of 90 min and an acceptance range of 18

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		The clear restrictive nature of the new proposal is further highlighted in the findings by Moore, where they reported the inherent variability of T_{max} for standard Ibuprofen product to a very large range of reported T_{max} mean, anywhere from 31 to 180 minutes. The coefficient of variation expressed in Percentage (CV%) is another parameter that can be used to better understand the extent of variability for a specific metric in relation to the mean and it is the ratio of the standard deviation to the mean often expressed as a percentage. We retrieved and, where unavailable, calculated (using the formula: CV% = (Standard Deviation/Mean [T_{max} or C_{max} or AUC_{0-t}])*100) the values of CV% for 16 PK studies providing data for Standard Ibuprofen reported in the Moore publication. Across all the studies considered, the CV% for T_{max} was consistently higher between studies compared to that of C_{max} and AUC_{0-t} as presented in Figure 1.	minutes, it means that samples need to be taken every 15 minutes, which is usual, and the median of the test products has to be found in the same sampling time or an adjacent sampling time, which is the criterion employed by some regulatory agencies until now to consider that T_{max} was comparable. Therefore, this new criterion does not imply any change. The CV is not critical because the decision is taken with the median without the calculation of 90% CI. Furthermore, the median is insensitive to outlier values (e.g. a profile with T_{max} at 180 min).

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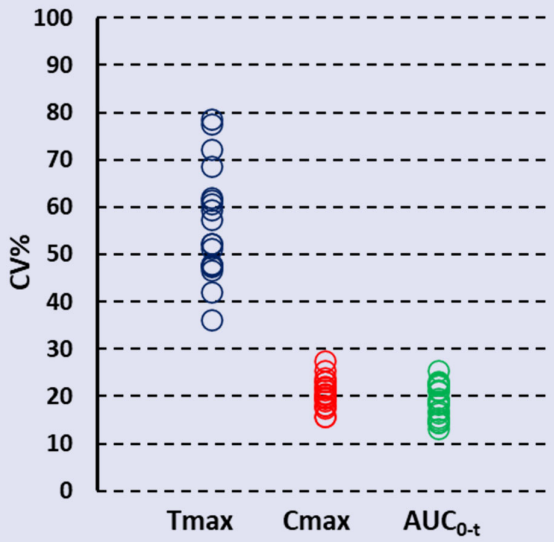
		Figure 1: Coefficient of variation (CV%) for Tmax, Cmax and AUC_{0-t} observed in 16 different studies reporting the pharmacokinetic profile for Standard Ibuprofen (n=19). The selection of studies is based on the studies discussed in Moore et al. 2014. ***References:*** *Internal Reckitt studies:* *NL0309, NL0405, NL0601, NL0703, NL0810, NL9709, NL9720, NL9809, R07-1009.* *Studies from scientific literature:* *Ceppi Monti N. et al. Arzneimittelforschung. 1992 Apr;42(4):556-9; Gontarz N. et al. Clinical pharmacy. 1987 May 1;6(5):413-6; Lenhard G. et al. Arzneimittel-forschung. 1990 Dec 1;40(12):1358-62; Lockwood G. F., et al. Clinical Pharmacology & Therapeutics. 1983 Jul;34(1):97-103; Schettler T., et al. Clinical Drug Investigation. 2001 Jan;21(1):73-8; Sörgel F. et al. International Journal of Clinical Pharmacology & Therapeutics. 2005 Mar 1;43(3); Walter K. et al. Arzneimittel-forschung. 1995 Aug 1;45(8):886-90.*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		 Additionally we believe the proposed criteria of Comparable median (≤20% difference) for T_{max} will likely push drug developers to use reference product with a later T_{max} as that will reduce the risk of missing the endpoint since the acceptable range will be broader. This has the potential to be detrimental to the patient as this could lead to an increase in the development and registration of slower formats. With slower format there is an increased risk of patient re-medicating due to a delay in the onset of analgesia. Which is	It is not agreed that slower formulations will be developed to use a wider acceptance range since quicker formulations are desired from a clinical and marketing point of view. It is agreed that what is to be avoided is that a generic product would have a different (slower) format than the reference which is the point of introducing the acceptance criteria.

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		we believe fundamentally opposed to the reason of the proposed draft T_{max} criteria. *References:* *1- Moore RA et al.. PAIN®. 2014 Jan 1;155(1):14-21.* **Proposed change:** In the absence of scientific rational, we oppose a T_{max} of 20%. We would like first of all to understand the reasons for proposing a T_{max} in the first place; we would be open to consider and discuss a proposed T_{max} which is scientifically grounded and justified based on efficacy and safety considerations.	
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	1	**Comments:** Because of the inherent variability of T_{max} the powering of the study to increase the chance to demonstrate Bioequivalence will require a larger number of subjects and therefore increase unnecessary exposure. Because of the inherent variability of T_{max} it will be important to reduce any external factor that are likely to increase even more the variability of this parameter and therefore will likely lead product developer to homogenize the subject demographics as much as possible. This seems to be counterintuitive in an era were industry and regulator are in favor of an approach driven by Diversity and Inclusion and the need for reduction of study results biased for gender or ethnicity among other biases.	**Not accepted.** As the comparison of T_{max} is conducted with median values without 90% CI the variability is not critical. The sample size required for the demonstration of bioequivalence for C_{max} and AUC should be sufficient to obtain a reliable and representative median T_{max}. In addition, the median is insensitive to outliers. It is agreed that frequent sampling may be required, but this is essential to ensure that the test and the reference have an equivalent biopharmaceutical quality and the onset of action if reached in a similar time with both products.

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		Because T_{max} is a continuous variable the need to meet such a restrictive endpoint will require for a lot of additional blood draw with tight intervals, (i.e. blood sampling every 3-5 minutes for product with predicted T_{max} around 30 minutes and every 15-18 minutes for product with predicted T_{max} around 90 minutes) to be added to the studies in order to ensure to capture T_{max} and not artificially increase the difference to more than 20% the T_{max} median of the Reference product. In other words, study sponsors might be worried that T_{max} can be missed if less blood sampling is done and be more confident if more blood sampling is carried out. **This will lead to credible feasibility and ethical concerns.**	Samples every 3 minutes are not necessary for products whose T_{max} is at 30 minutes as explained above. Every 5 minutes around T_{max} is enough. Every 15 minutes is the standard frequency, therefore, there is no critical change. No ethical concern is anticipated if the volume of blood is not excessive. The present bioanalytical methods allow to sample less than 300 ml of blood in total in studies with up to 25 samples. Therefore a few more samples for a proper characterisation of T_{max} and C_{max} are not considered an ethical problem.
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	1	**Comments:** The current regulatory framework considers salts and acids under the same immediate release oral ibuprofen category. This new criterion is written with the intent of comparing like with like but does not take into account the rest of the regulatory framework where there are restrictions of the available reference products that can be used. According to Eudralex Volume 2A, "A generic product and a reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopoeia. Furthermore, Article 10(2)(b) of the amended Directive provides that the various immediate release oral forms, which would include tablets, capsules, oral solutions and suspensions, are	**Not accepted.** It is agreed that different salt forms can be considered as generic according to the current EU legislation, if they are shown to be bioequivalent. This product specific guideline defines the criteria to be fulfilled to be considered as bioequivalent. There are no restrictions on the available reference product that can be used. Any dosage form with a complete dossier can be used. The different dosage form can be generic only if they are immediate release and oral dosage forms. For ibuprofen, arginine, lysine, and sodium salts, liquid and solid dose formulations, orodispersible tablets and any other immediate release format could be considered the "same" from a regulatory and legal basis point of

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		considered to be the same pharmaceutical form for the purposes of Article 10." This means that for ibuprofen, arginine, lysine, and sodium salts, liquid and solid dose formulations, orodispersible tablets and any other immediate release format are considered the "same" from a regulatory and legal basis point of view. Under the new proposed guideline, it could be expected that all these diverse formulations have comparable T_{max}. This new criterion could force generic applications to develop very narrowly confined formulations to ensure bioequivalence, it reduces innovation and development of new pharmaceutical forms which are beneficial to the consumer/patient, as each would potentially require either multiple bioequivalence studies to meet the narrow 20% window or efficacy studies to support, leading to an unnecessary clinical and ethical burden. **Proposed change:** In the absence of scientific rational, we oppose a T_{max} of 20%. We would like first of all to understand the reasons for proposing a T_{max} in the first place; we would be open to consider and discuss a proposed T_{max} which is scientifically grounded and justified based on efficacy and safety considerations.	view, but bioequivalence has to be demonstrated between them. It is expected that the different salts (arginine, lysine, and sodium salts) will be bioequivalent between them if they are formulated in the same or comparable dosage forms. But they might be unable to be bioequivalent if the dosage form is notably different (e.g. solution/suspension vs. tablet). See previous comments on the rationale.
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20%	1	**Comments:** In our opinion, the inclusion of T_{max} in the primary endpoint analysis is not justified for ibuprofen and should be avoided. According to the "Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr**, the	**Not accepted.** See response to previous comments.

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difference) and range for T_{max}.		evaluation of T_{max} should be performed when the rapid release of the substance is clinically relevant and of importance for the onset of action or is related to adverse events (AE). Rapid onset of action is usually of importance for life-saving products, and ibuprofen is not one of those. Also, there is no data showing that any AEs could be related to the rapid release of the substance from the formulation. **Therefore, for a standard pain-killer like ibuprofen, in immediate release oral formulations, it is recommended to keep the requirements as they are presented in the abovementioned guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**, that is the statistical evaluation of T_{max} should not be required.** Previous comments: In this section, it is proposed that the median and range for T_{max} should be "comparable". On the other hand, as it was stated above, the principle "Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr** states that in general, the statistical evaluation of T_{max} is not required. Previous outcome: T_{max} is not an end point to be included in the statistical analysis but a comparison of the values should be made and any differences discussed in the context of the application. In the overview of consultation comments for the first version of this (EMA/CHMP/730723/2017), the issue of T_{max} was	

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		already discussed in very similar terms, and it was concluded that T_{max} was "not an end point to be included in the statistical analysis but a comparison of the values should be made and any differences discussed in the context of the application**".** **We believe this view is still valid and no new relevant scientific evidence or specific product safety signal on product approved on the basis of the current guideline that would supports a change to a more restrictive fixed comparison value between T_{max}.** **Proposed change:** In the absence of scientific rational, we oppose a T_{max} of 20%. We would like first of all to understand the reasons for proposing a T_{max} in the first place ; we would be open to consider and discuss a proposed T_{max} which is scientifically grounded and justified based on efficacy and safety considerations.	
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	1	**Comments:** The rationale behind the development of product-specific bioequivalence guidance, according to the Concept paper on the development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013), is to "facilitate transparent, predictable and scientifically robust assessment in future marketing authorisation procedures" and "to enable a consistent approach to the assessment of applications based on bioequivalence data, particularly generic applications, across all submission routes.	**Not accepted.** See response to previous comments.

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		Product specific bioequivalence guidelines are available for only a limited number of active ingredients, predominantly focusing on prescription drugs for serious conditions such as cancer drugs (Abiraterone, Alectinib, Cabozantinib, Capecitabine, Vismodegib, Sirolimus, Sunitinib, Lapatinib), anti-coagulants (Acenocoumarol, Apixaban), antidepressants (Agomelatine), blood pressure drugs (Aliskiren), antipsychotics (Asenapine, Paliperidone), epilepsy drugs (Zonisamide), and antibiotics (Telithromycin). Previous consultation comments: According to the "Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr**, the evaluation of T_{max} should be performed when the rapid release of the substance is clinically relevant and of importance for the onset of action or is related to adverse events (AE). Rapid onset of action is usually of importance for life-saving products (such as those listed above), and ibuprofen is not one of those. Also, there is no data showing that any AEs could be related to the rapid release of the substance from the formulation. Therefore, for a standard painkiller like ibuprofen, in immediate release oral formulations, it is recommended to keep the requirements as they are presented in the abovementioned guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**, that is the statistical evaluation of T_{max} should not be required.	

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		Proposed change: In the absence of scientific rational, we oppose a T_{max} of 20%. We would like first of all to understand the reasons for proposing a T_{max} in the first place; we would be open to consider and discuss a proposed T_{max} which is scientifically grounded and justified based on efficacy and safety considerations.	
19 "Bioequivalence assessment" header	2	**Comments:** The updated product specific bioequivalence guideline (PSBGL) for Ibuprofen proposes the introduction of the definition of comparable median for T_{max} as ≤ 20% difference, still recommending the comparability of the range of T_{max}. Ibuprofen is rapidly absorbed when administered orally, with T_{max} generally attained 1-2 h after administration of solid formulations. However, T_{max} is, by definition, the time to reach maximum concentration (C_{max}), not the time of onset of drug efficacy. To account for the evaluation and the comparison of the actual onset of action among different ibuprofen formulations, higher relevance should be given to the time required to achieve acknowledged active plasma concentrations (i.e., Tonset) for the proposed indication. Relevant scientific literature should be considered as a suitable basis to be used as a reference for the scope. For instance, for analgesia, Stillings et al. (2003) indicate that "*signs of pain relief produced by a 400 mg standard dose of ibuprofen would begin to manifest at plasma levels of between 5 and 10 µg/ml*". Later, Mehlisch et al. (2013) confirmed	**Not accepted.** It is agreed that T_{max} is not the time of onset of action, but by ensuring that T_{max}, C_{max} and AUC are equivalent, the onset of action will be also equivalent. It might be possible to define a new parameter (Tonset) as the time to achieve acknowledged active plasma concentrations. However, this product specific guideline has to be developed in line with the existing guideline on the investigation of bioequivalence. Therefore, new PK parameters cannot be included, and we can only clarify how to conduct the T_{max} comparison and define the acceptance criteria.

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		almost the same range, indicating that "*The first confirmed signs of analgesia were observed at 20 min post dosing, when the average plasma concentration for patients receiving 400 mg ibuprofen was 8.4 µg/ml. This analysis suggests that the onset of analgesia occurs at ibuprofen plasma concentrations between 6.8 and 10.1 µg/ml.".* Taken together, these and further available references could lead to the identification of a univocal threshold/range for the computation of T_{onset}, to be compared among the different ibuprofen formulations (especially for the fast-acting ones) to support T_{max} evaluation.	
19 "Bioequivalence assessment" header	2	**Comments:** The updated product specific bioequivalence guideline (PSBGL) for Ibuprofen sets as comparable median T_{max} values with a difference ≤ 20%, with no clear definition of how to evaluate the comparability of the ranges of T_{max}. From a statistical point of view such an evaluation would hardly be sound, being guided by subjective assessments. More precise criteria (e.g., subjects' distribution within the range) would be helpful for the scope.	**Not accepted.** See responses to previous comments.
23-28	2	**Comments:** The current text of the PSBGL for Ibuprofen describes the possibility of opting for a BCS-based biowaiver approach instead of performing an in-vivo clinical trial when the drug's BCS classification allows so (i.e., for class I and III substances).	**Not accepted.** It is agreed that ibuprofen is not a BCS class I or III drug. The use of IVIVC is always possible, but it is not within the scope of this PSBGL to discuss this possibility.

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		However, ibuprofen does not fall within this case, being commonly considered a low solubility compound, thus with no/low possibility of application of a BCS-based biowaiver. Approaches alternative to in vivo clinical trials and in vitro BCS biowaivers could tentatively be taken into consideration, with particular reference to IVIVC/PBPK models, allowing for the comparison of compounds both in-vitro and by means of simulations.	The use of PBPK virtual BE studies is out of the scope of this PSBGL.
Table 'Requirements for bioequivalence demonstration' Line 'Bioequivalence assessment'	3	**Comment:** 'T' is the SI symbol for the absolute temperature. **Proposed change:** Use the correct SI symbol 't' for time, at least for consistency with the overarching guideline. [1] 1. EMA (CHMP). *Guideline on the Investigation of Bioequivalence*. CPMP/EWP/QWP/1401/98 Rev.1/Corr. London, 20 January 2010.	**Accepted.**
Table 'Requirements for bioequivalence demonstration' Line 'Bioequivalence assessment'	3	**Comment:** 'Comparable […] range for T_{max}'. Like the mean, the range has a breakdown point of zero, i.e. a *single* extreme value distorts the range. Hence, a *confirmatory* assessment of the range is not contained in the statistical toolbox. It must only be assessed in an *exploratory* data analysis. Let us consider three formulations (two tests T1, T2 and one reference R) in a study of an arbitrarily large [sic] sample size. All T_{max} values except one are identical: The sets of observed T_{max} values are R {1,…,1.25}, T1 {1,…,1.5}, T2 {1,…,1}. Their	**Not accepted.** The wording of the current Guideline on the Investigation of Bioequivalence in this topic is difficult to implement: "*A statistical evaluation of T_{max} is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median T_{max} and its variability between test and reference product*".

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		respective ranges are 0.25, 0.5, and 0. Are these ranges 'comparable', and if yes, why? If they are 'not comparable', why? Is T1 'worse' than R because its range is larger? Is T2 'better' than R because its range is smaller (actually zero)? Of course, such a comparison is absurd. Naturally, the medians are identical.	The purpose of this updated PSBGL is to clarify how to assess or compare the medians with an objective acceptance range. The assessment of the range is more subjective. If all the values except one are the same, the ranges would be considered acceptable. Therefore, only if differences are evident and worse for the test product, the range could be used for a regulatory decision.
Table 'Require-ments for bio-equivalence demonstration' Line 'Bioequivalence assessment'	3	**Comment:** It was somewhat surprising that in the first draft of the guidance "Comparable median and range for T_{max}" was stated [1] and the agency responded to comments by stakeholders "T_{max} is not an end point to be included in the statistical analysis but a comparison of the values should be made and any differences discussed [sic] in the context of the application (see later)". [2] Regrettably nothing was given *later*. This response could be understand that a comparison of T_{max} should only be discussed. However, in the adopted guidance [3] "Comparable median and range for T_{max}" is still given in 'Bioequivalence assessment'. 1. EMA (CHMP). *Ibuprofen 200 - 800 mg oral use, immediate release formulations product-specific bioequivalence guidance*. EMA/CHMP/356876/2017. 20 July 2017. 2. EMA (CHMP). *Overview of comments received on 'Ibuprofen 200 – 800 mg oral use, immediate release formulations product-specific bioequivalence guidance'*. EMA/CHMP/730723/2017. 31 May 2018.	**Not accepted.** T_{max} is considered a primary PK parameter for drugs where the onset of action is clinically relevant according to the Guideline on the Investigation of Bioequivalence. Therefore, it must be included under bioequivalence assessment, but this assessment is performed without a statistical inference approach since it is not based on 90% CI, but on the difference between medians. Consequently, the response "T_{max} is not an end point to be included in the statistical analysis but a comparison of the values should be made" was correct. The objective of the present review of the PSBGL is not to change the requirements of the existing Guideline on the Investigation of Bioequivalence, but to clarify how to interpret it. As the discussion of any difference in the context of the application is subjective, the present update of the PSBGL intends to define an objective criterion to avoid arbitrations.

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		3. EMA (CHMP). *Ibuprofen oral use immediate release formulations 200 - 800 mg product-specific bioequivalence guidance.* 31 May 2018. The *true* T_{max} follows a continuous distribution indeed. Furthermore, it is on a ratio scale (i.e. with a true zero). However, due to the sampling schedule, the *observed* T_{max} gets discretized, i.e. results in data on an ordinal scale. The only [sic] allowed operations for ordinal data are addition, subtraction, and ranking. To be clear: Multiplication and division are *not* allowed. Hence, calculating a ratio (expressed as a percentage) is statistically flawed from the start. The distribution of observed T_{max} is skewed to the right, which "can be attributed to the asymmetry of the observed concentrations around the peak. The concentrations rise more steeply before the peak than they decline following the true maximum response. Consequently, it is more likely that large observed concentrations occur after than before the true peak time." [4] 4. Tóthfálusi L, Endrényi L. *Estimation of* C_{max} *and* T_{max} *in Populations After Single and Multiple Drug Administration.* J Pharmacokin Pharmacodyn. 2003; 30(5): 363–85. doi:10.1023/b:jopa.0000008159.97748.09. An example from our files; pooled IR data of seven studies:	Regarding the comment on calculating the ratio of data on an ordinal scale is not an allowed operation. Hence, the '±20% difference in medians' criterion is statistically flawed, the ordinal scale is due to the discrete time schedule, whereas the continuous "true T_{max}" can be considered as the target of estimation. Hence, calculating a ratio as an estimation of the true T_{max} ratio still makes sense even if estimation may not be optimal due to the discrete sampling time points' estimation. Obviously, the denser the sampling schedule the more accurate the estimation will be, but for practical reasons the number of sampling time points is limited. However, as the '±20% difference in medians' criterion might still be considered as flawed since it violates the principle of symmetry (i.e. the requirement that test should be equivalent to reference if and only if reference is equivalent to test) it is therefore slightly modified (or more precisely specified) to a 80%–125% rule. An acceptance range (delta) is pre-defined in this PSBGL for T_{max}, because T_{max} is compared only in those cases where it is clinically relevant for the onset of action. It is agreed that from an inferential/statistical point of view, the use of a non-parametric 90% confidence interval is more correct. But this correct statistical methodology is not implemented in the PSBGL because

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		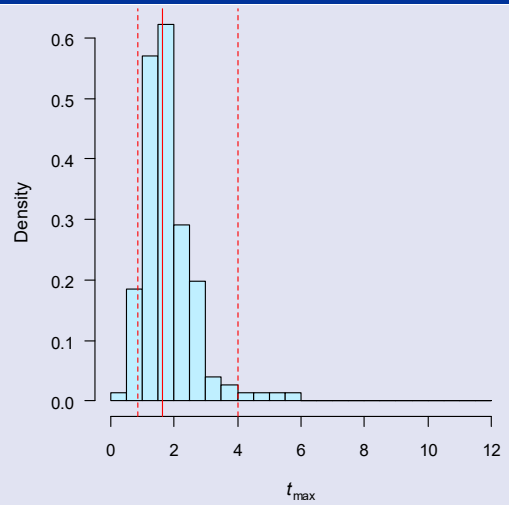 Red line median, red dashed lines 2.5 and 97.5 percentiles. As expected, the distribution of T_{max} is heavily skewed to the right (skewness +0.771), thus confirming the theoretical considerations. [4] It must not be forgotten that comparative bioavailability of conventional PK metrics (*AUC*, C_{max},…) is based on a *clinically relevant difference* Δ, leading with the common 20% in a *multiplicative* statistical model to the BE-limits $\{\theta_1,\theta_2\}=\{100(1-\Delta),100(1-\Delta)^{-1}\}=\{80\%,125\%\}$. Consequently, a similar approach should be applied to T_{max}, i.e. if – and only if – clinically relevant, a certain Δ has to be pre-specified, which leads in an *additive* statistical model to the BE-limits $\{\theta_1,\theta_2\}=\{-\Delta,+\Delta\}$.	the PSBGL is in line with the overarching Guideline on the Investigation of Bioequivalence. The comparison of the medians does not intend to preserve the type 1 error but to exclude formulations with different onset of action. The definition of ≤ 20% (80–125%) as acceptance range intends not to reject products where T_{max} is not excessively rapid and the sampling time around T_{max} is very frequent. For example, if samples are taking every 5 minutes and T_{max} occurs after 2 h, a 10-minute difference in a non-adjacent sampling time is acceptable, but it would be rejected if the samples are required to be adjacent. This criterion reinforces the idea that sampling times around T_{max} should be frequent enough to characterise C_{max} appropriately. If T_{max} is expected after 30 minutes, samples every 5 minutes are required. It is not the objective to take samples every 2–3 minutes, even if this is necessary for some orally inhaled products and it is known to be feasible. Regarding the comment on the tight sampling schedule, samples every 5 minutes are feasible.

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		Given the fact that data are discrete on an ordinal scale, the only valid statistical approach for comparing two formulations is by an appropriate nonparametric method. [5–10] 5. Hauschke D, Steinijans VW, Diletti E. *A distribution-free procedure for the statistical analysis of bioequivalence studies.* Int J Clin Pharm Ther Toxicol. 1990; 28(2): 72–8. PMID:2307548. 6. Basson RP, Cerimele BJ, DeSante KA, Howey DJ. *T_{max}: An Un-confounded Metric for Rate of Absorption in Single Dose Bio-equivalence Studies.* Pharm Res. 1996; 13(2): 324–8. doi:10.1023/A:1016019904520. 7. Basson RP, Ghosh A, Cerimele BJ, DeSante KA, Howey DC. *Why Rate of Absorption Inferences in Single Dose Bioequivalence Studies are Often Inappropriate.* Pharm Res. 1998; 15(2): 276–9. doi:10.1023/a:1011974803996. 8. Hauschke D, Steinijans V, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: Wiley; 2007. p. 97–100. 9. Chow S-C, Liu J-p. *Design and Analysis of Bioavailability and Bioequivalence Studies*. Boca Raton: Chapman & Hall/CRC Press; 3rd ed. 2009. p. 109–19. 10. Jones B, Kenward MG. *Design and Analysis of Cross-Over Trials.* Boca Raton: Chapman & Hall/CRC Press; 3rd ed. 2015. p. 68–96. As an aside, a nonparametric test was recommended by the EM(E)A for 19 years and is currently recommended in Argentina, Japan, South Africa, and by the WHO. A statistical comparison of T_{max} was never – and is not – required by the FDA and Health Canada.	Obviously, the tighter the sampling schedule the powerful (and accurate) a statistical test will be. Nevertheless, and more important, the power of a statistical test (usually be performed using a confidence interval), and consequently the sample size needed, will depend on the requested equivalence range and significance level (the allowed type-1 error rate). Equivalence range could be wider than the range that is applied for point estimate. Also, the allowed type-1 error rate (or equivalently, the coverage probability of the confidence interval) may be less strict than for AUC and C_{max}. This would allow for assessing the consumers risk for T_{max} but on a different level than for AUC and C_{max}. Still an agreement on both, equivalence range and significance level to be used, may be difficult to achieve. It is considered that while the Hodges-Lehmann estimator is an adequate estimator to compare T_{max} of Test (generic) and Reference (innovator) products, it estimates the median difference as compared to the current approach of comparable median and range for T_{max} which estimates the difference in medians. The current approach has been a requirement of the ibuprofen product-specific guideline since 2018 and the present revision of the product specific guideline concerns better defining what is meant by comparable and not introducing a new method particularly one for which EMA experience in regulatory submissions is

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		In the following we explored both the '±20% difference in medians' criterion as well as with the nonparametric CI inclusion approach, where $\theta_1 = -\Delta$ and $\theta_2 = +\Delta$ $H_0 : \mu_T - \mu_R \not\subset \{\theta_1, \theta_2\}$ vs $H_1 : \theta_1 < \mu_T - \mu_R < \theta_2$ We simulated individual subject profiles of 24 subjects in 2,500 studies in a three-arm parallel design.* * Only for speed reasons. Runtime of a couple of hours on a work-station. Simulating a crossover design takes days. The absorption rate constants k_{01} of three formulations, i.e. R (reference), A (fast), and B (slow) were obtained by numerically solving $\log_e(k_{01} \cdot t_{½} / \log_e(2)) / ((k_{01} - \log_e(2)/t_{½})) - t_{max} = 0$ for k_{01} with $t_{½}$ = 1.93 h and T_{max} 1 h, 48 min, and 72 min, respectively. Elimination, fraction absorbed, and volume of distribution were identical. Error distributions were uniform for f (0.6–1), lognormal for V (CV 50%), k_{01} (CV 35%), k_{10} (CV 40%). Distribution of the analytical error was normal with a CV of 5% of the simulated concentration. The LLOQ was set to 5% of $C_{max(R)}$. The sampling schedule was every five minutes until two hours, 2.25, 2.5, 3, 3.5, 4, 6, 9, 12, and 16 hours (34 time points). In the nonparametric test Δ was set to 12 min, mimicking the '±20% difference in medians' criterion. Since $\mu_A = \theta_1$ and $\mu_B = \theta_2$, the number of passing studies divided by the number of simulations represents the empiric Type I Error.	limited. Therefore, the continued use of the current approach is recommended until the BE requirements are updated with M13. The proposed ≤ 20% difference should be understood as 80–125% in order to be symmetrical. Regarding the comment on the inconsistency with the in vitro approach, we do not agree necessarily since the in vivo approach is not considered an alternative approach in all settings but only allowed in specific circumstances. A BCS biowaiver approach is not acceptable because ibuprofen is a BCS class II. The in vitro approach based on a BCS biowaiver is not applicable because it is a BCS class II drug. The reference to the paper by Potthast et al. is outdated. The WHO guideline that included this possibility was updated many years ago to remove the BCS biowaiver of BCS class IIa drugs. To conclude: • It is agreed that assessing the consumer risk would require a statistical test corresponding to a confidence interval approach. However, the guideline does not require the calculation of the non-parametric 90% CI because it would increase notably the required sample size. • The comparison of the medians is intended to exclude products with different onset of action,

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		The '±20% difference in medians' criterion is not a statistical test. However, one can expect for both test treatments an equal chance to pass or fail because $\mu_A = 0.8 \times \mu_R \rightarrow \tilde{t}_{max(A)} < 0.8 \times \tilde{t}_{max(R)} \approx \tilde{t}_{max(A)} \geq 0.8 \times \tilde{t}_{max(R)}$ as well as $\mu_B = 1.2 \times \mu_R \rightarrow \tilde{t}_{max(B)} \leq 1.2 \times \tilde{t}_{max(R)} \approx \tilde{t}_{max(B)} > 1.2 \times \tilde{t}_{max(R)}$ Confirming [4] and our observations of IR formulations, the distributions were positively skewed (R +0.674, A +0.778, B +0.750). The empiric Type I Errors were controlled (A vs R 0.0532, B vs R 0.0368; i.e. below the significance limit of the binomial test 0.0578). Surprisingly in the '±20% difference in medians' criterion passing-rates were larger than the expected 50% (A 57.9%, B 55.0%). It is questionable, whether for a reference formulation with a T_{max} of one hour a Δ of twelve minutes has any clinical relevance. Following the logic of the '±20% difference in medians' criterion, for a reference with a T_{max} of 30 minutes a Δ of six minutes is practically unachievable even with an logistically unrealistic sampling every two minutes. Furthermore, sample size estimation would require subject simulations with an in-depth knowledge of not only the drug but also of the formulations (absorption rate constant, lag time). Whereas PK parameters might be in the public domain, their variances almost never are. In a study in a replicate design the reported median T_{max} was 45 minutes after both administrations. It should be noted that range of T_{max} after the 1st administration was 0.25–4 h (CV 94.3%) and after the 2nd 0.5–2 h (CV 62.3%). [11]	because a statistically sound method requires excessive sample size. • Samples every 5 minutes are feasible. • Asking for a non-parametric 90% CI is more restrictive. • Although it is agreed that the non-parametric 90% CI for the T_{max} difference is more correct methodologically, its use was discarded by the Guideline on the Investigation of Bioequivalence and this PSBGL cannot implement it against the guideline. • It is agreed that the clinically relevant delta (acceptance range) should be fixed by the agency. Specific equivalence ranges may indeed be discussed. Still, it appears useful to first establish a default range that could be adapted for specific substances. The definition of a clinically relevant acceptance range for each specific drug is not feasible and it is not in line with the Guideline on the investigation of bioequivalence. Requiring T_{max} as a primary PK metric in vivo is not inconsistent with the in vitro approach because when in vitro dissolution is used for a waiver of the in vivo study, it is assumed not only that C_{max} and AUC will be equivalent but also T_{max}. In addition, the in vivo approach is not considered an alternative approach in all settings, but only allowed in specific circumstances.

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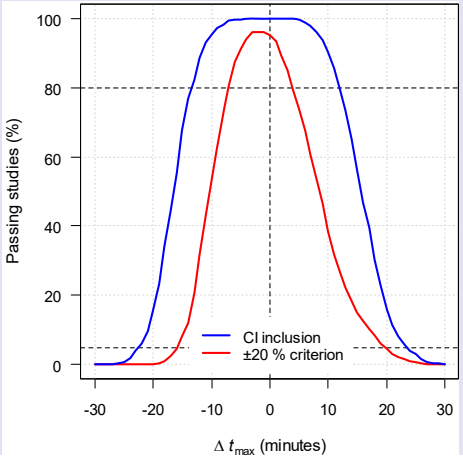
		11. Wagener HH, Vögtle-Junkert U. *Intrasubject variability in bio-equivalence studies illustrated by the example of ibuprofen.* Int J Clin Pharmacol Ther. 1996; 34(1): 21–31. PMID:8688993. The sample size in a parallel design would require for C_{max} with its CV of 25.4% for an assumed T/R-ratio of 0.95 56 subjects and for a T/R-ratio of 0.95 114 subjects to achieve at last 80% power. We simulated 1,000 studies* with 28 subjects / arm where the T_{max} of the reference formulation was 45 minutes and the T_{max} of test formulations varied from 15 (ΔT_{max} −30) to 75 (ΔT_{max} +30) minutes. * For speed reasons. Runtime 4½ days on a workstation. Simulating a crossover design takes weeks. The sampling schedule was every five minutes until 1.5 hours, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, and 12 hours (33 time points). In the CI inclusion approach Δ was set to 20 minutes.  	When products have the same or similar T_{max}, it is expected that the sample size required to show equivalence in C_{max} will be able to provide an accurate estimation of T_{max}. Compliance with an arbitrary limit of 20% for the difference in medians is considered feasible and in line with the guideline on the investigation of bioequivalence. Obviously, the closer the assumed PK model to the data generating model the more precise the sample size estimation will be. However, sample size estimation is always based on assumptions. For specific active substances, it might be possible to assume a Population PK model that is reasonably close. The Guideline on the investigation of bioequivalence will be updated by the ICH in M13. The proposal could be considered in an updated version. The population median as a population parameter has no variability since it is a fixed parameter. The empirical median as an estimation method is variable according to the sampling distribution, which can be described by the corresponding standard error of the median.

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		As expected, the power curve of the CI inclusion approach is symmetrical around zero. With a more restrictive Δ of 15 minutes, power for ΔT_{max}=−10 min would drop from 95.3% to only 60.5%. The power curve of the '±20% difference in medians' criterion is asymmetrical and its maximum is shifted to the left. The '±20% difference in medians' criterion is also extremely restrictive: At least 80% power is only achievable for ΔT_{max} of −7 to +4 minutes. Due to the asymmetry, for any given ΔT_{max} a negative value has higher power than a positive one. That means, a 'faster' test is more likely to pass than a 'slower' one. If, say, ΔT_{max}=−5 min, 90.5% of studies will pass but if ΔT_{max}=+5 min, only 74.8%. Or more pronounced: A test product with T_{max} 43 min (ΔT_{max}=−2 min) has with 96.0% a higher chance of passing than one with T_{max} 45 min (ΔT_{max}=0 min) with 94.2%. This weird behaviour is due to falsely calculating a ratio while keeping symmetrical limits. Apart from the not allowed operation on an ordinal scale it is similar to keeping the BE-limits at 80–120% (common in the 1980s) when analyzing log-transformed PK metrics. Then power curves would be asymmetrical as well, with the maximum power at a T/R-ratio of 97.8% instead of at 100%. Since the sampling interval of [11] was insufficient, we fitted a population PK model, allowing to generate profiles for arbitrary sampling intervals (we compared the original sampling with every 15, 10, 5, and 2 minutes). While the difference in medians increased (from the identical 45 minutes in the original sampling to 7 minutes with 2 minute sampling), all	

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		would pass the '±20% difference in medians' criterion. However, the CI inclusion approach showed a different picture. It was impossible to demonstrate BE with a Δ of 12 minutes. With Δ of 26 minutes only profiles with Δ10 minutes sampling passed. Δ had to be increased to 30 minutes in order that profiles with 15 minutes sampling passed. Recall that in this study the reference was compared to itself. It is a widespread misconception that the Wilcoxon signed-rank test (for paired samples) and the Mann–Whitney U test (for independent samples) compare medians. The former employs the Hodges-Lehmann estimator, whereas the latter compares the median of the difference between a sample from *x* and a sample from *y*. Both are permutation tests and thus, computationally intensive. Strictly speaking, they give unbiased estimates of a shift in location only if distributions are identical (though not necessarily symmetrical). However, in well-controlled studies this is likely the case. [5] In our simulations distributions were similar (skewness +0.674 to +0.778). Recall that in parametric methods independent and identical distributions are assumed as well. Furthermore, in a crossover study evaluated by an ANOVA homoscedasticity (equal variances) is assumed. If these assumptions do not hold, the residual error is inflated, increasing the producer's risk – which is not a regulatory concern. The same is likely in nonparametric approaches. Alternatives not requiring identical distributions [12–14] have not been assessed for their operating characteristics in a BE-setting so far.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		12. Brunner E, Munzel U. *The Nonparametric Behrens-Fisher Problem: Asymptotic Theory and a Small-Sample Approximation.* Biom. J. 2000; 42(1): 17–25. doi:10.1002/(SICI)1521-4036(200001)42:1%3C17::AID-BIMJ17%3E3.0.CO;2-U. 13. Neubert K, Brunner E. *A studentized permutation test for the non-parametric Behrens–Fisher problem.* Comput Stat Data Anal. 2007; 51(10): 5192–204. doi:10.1016/j.csda.2006.05.024. 14. Wilcox RA. *Introduction to Robust Estimation and Hypothesis Testing.* London: Academic Press; 4th ed. 2017. p. 192–8. A BCS-based biowaiver is acceptable as an alternative to the *in vivo* approach and its conditions are outlined one of the FIP's biowaiver monographs. [15] 15. Potthast H, Dressman JB, Junginger HE, Midha KK, Oeser H, Shah VP, Vogelpoel H, Barends DM. *Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ibuprofen.* J Pharm Sci. 2005; 94(10): 2121–31. doi:10.1002/jps.20444. In other words, in the *in vitro* approach it would be readily acceptable to assess the risk of bioinequivalence based on studies in the public domain without T_{max} as a primary PK metric. To conclude: • Calculating the ratio of data on an ordinal scale is not an allowed operation. Hence, the '±20%	

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		difference in medians' criterion is statistically flawed. ○ Since it is not a valid statistical test, the consumer risk cannot be assessed. ○ It would require a tight sampling schedule, which is not realistic for products with an early T_{max}. ○ It is extremely restrictive and hence, would require prohibitively large sample sizes. • The confidence interval inclusion approach is based on a valid test for differences in T_{max}, and hence, controls the consumer risk. ○ The clinically relevant Δ should be fixed by the agency. Sample size estimation requires *full* information of the PK of the drug / drug products and a suitable PK model in order to ○ perform simulations. If this information is not available, strictly speaking the requirement "The number of subjects to be included in the study should be based on an appropriate sample size calculation" [EMA (CHMP). *Guideline on the Investigation of Bioequivalence*. CPMP/EWP/QWP/1401/98 Rev.1/Corr. London, 20 January 2010.] cannot be fulfilled. Then a reasonably large pilot study has to be performed in order to establish a valid (Population) PK model. ○ It is an open question, what might by clinically relevant for a drug product with multiple	

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		indications. In the indication 'rapid relieve of pain' Δ might be smaller than for treatment of fever in paediatrics. • Requiring T_{max} as a primary PK metric in the *in vivo* approach is inconsistent with the acceptable risk assessment in the *in vitro* approach. By the way, the statement "[…] if rapid release is claimed to be clinically relevant […] there should be no apparent difference in median T_{max} and its variability between test and reference product" in [*Guideline on the Investigation of Bioequivalence*] deserves an update in its next revision as well. What might 'apparent' be? Furthermore, the median is a statistic (one of many *estimators* of location) and its value is an *estimate* (i.e. a certain number). It does not have a 'variability', only the sample has one. **Proposed change:** T_{max} should be compared by a nonparametric method. The 90% confidence interval should lie within ± *X* minutes.* * The value of *X* to be stated in the guidance should be based on the clinically relevant Δ and depends on the PD property caused by of the reference formulation. However, for consistency with the *in vitro* approach we suggest to remove the comparison of T_{max} completely.	
Table included as line 19, Table row	4	**Comments:** The table in this section includes under 'Main pharmacokinetic variables'; the T_{max}.	**Not accepted.** As the onset of action is relevant for analgesic drugs, T_{max} needs to be considered as a primary PK parameter.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Bioequivalence assessment		**Would you please clarify if the intention was to make the T_{max} one of the primary endpoints of the study**? In our opinion the inclusion of T_{max} in the primary endpoints is not justified for Ibuprofen. The main over-arching bioequivalence guidance (CPMP/EWP/QWP/1401/98 Rev 1) states that no statistical evaluation is required, except for products where rapid release is claimed to be clinically relevant. Rapid onset of action is usually considered of importance for life saving medicines. We believe that a standard OTC administration for pain relief doesn't fit such a category. In addition, Ibuprofen's clinical effect does not need to reach maximum plasma concentration (C_{max}) as the therapeutic concentration is much lower than C_{max}. Therefore, the time to reach C_{max} (i.e. T_{max}) is of much less significance than the time to reach a therapeutic concentration. This means that T_{max} in the context of OTC pain medication is of little relevance unless a rapid onset of action is being claimed in which case T_{max} may indicate a quicker time to therapeutic levels. Additionally, there is no data supporting any adverse events related to the rapid release of Ibuprofen. T_{max} generally reflects the timing of major absorption events for orally administered drugs, and it is assumed that the main goal of T_{max} language in the guidance is to help ensure that major absorptive events occur over similar time frames for the test and reference product. While Ibuprofen sometimes occurs	Onset of action is not only relevant for life-saving medicines. As stated above, the time to reach active concentration could be used instead of T_{max}, but the PSBGL cannot implement parameters that are not in line with the existing Guideline on the investigation of BE. T_{max} together with C_{max} are used as a surrogate of rate of absorption and if rate of absorption is similar, the onset of action will be similar. Therefore, T_{max} is used as a surrogate to assess equivalence in the onset of action in line with the requirements of the Guideline on the investigation of bioequivalence.

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		in one single event, it is frequently split into 2 or more smaller absorptive events, separated by intervals of diminished absorption. This is not formulation dependant. From the literature it is also widely known that ibuprofen has a variable absorption profile. From the 70 (finalised) 'Product-Specific bioequivalence guidance' documents issued, only 4 products include a specific reference to T_{max}, and 3 of these are currently under consultation. For the 2 PSBGLs for analgesics, Paracetamol (a highly soluble BCS Class 1 drug) and Ibuprofen, these don't meet the criteria as defined in the overarching BE guidance as stated above. For Tadalafil (a product for erectile dysfunction) and Paliperidone (an anti-psychotic), rapid onset of action may be clinically relevant. **Proposed change:** T_{max} to be removed from the 'Main Pharmacokinetic Variables' within the newly proposed guidance but remains part of the 'Bioequivalence assessment' as 'comparable median and range for T_{max}'. Include an assessment as per general BE guidance detailed on p 15/27, 4.1.8" if *rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median T_{max} and its variability between test and reference product*"	

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td>Table included as line 19, Table row Bioequivalence assessment</td><td>4</td><td>Comment:
The table in this section of the proposed guidance includes” Comparable median (≤ 20% difference)” as a new parameter. In order to provide meaningful comment relating to this update, more information is required as to how the limit of 20% was determined to be the appropriate value.
T_{max} is a pharmacokinetic parameter that for orally administered ibuprofen is highly variable both within and between subjects.

T_{max} data presented in various studies supporting approved products (available in MRI Index/PAR) shows variability reported in different studies:
• Reference product (Brufen® (Ibuprofen) 200 mg tablets of Abbott Laboratories Limited), T_{max}, presented shows interindividual variability within the same study and variability comparing mean T_{max} in the different studies.

<table>
<tr><th></th><th colspan="3">Reference</th><th>Test</th></tr>
<tr><td></td><td>Ibuprofen</td><td>T_{max} (h)</td><td>T_{max} (h)Range</td><td>T_{max} difference (%)</td></tr>
<tr><td>SE/H/2058/01-01/DC_study1</td><td>R/S</td><td>1.63</td><td>0.75-5.00</td><td>0</td></tr>
<tr><td>SE/H/2058/01-01/DC_study2</td><td>R/S</td><td>1.38</td><td>0.75-5.00</td><td>0</td></tr>
<tr><td>NL/H/2109/001</td><td>R/S</td><td>1.75</td><td>0.50-4.00</td><td>0</td></tr>
<tr><td colspan="2">Interstudy T_{max} Variability</td><td colspan="2">21%</td><td></td></tr>
<tr><td>MT/H/0166/000</td><td>R</td><td>1.75</td><td>0.50-3.50</td><td>25</td></tr>
</table>
</td><td>Not accepted.

20% has been defined arbitrarily in line with the usual acceptance range for C_{max} and AUC, taking into account that it is a limit for a difference between the medians and not for the non-parametric 90% CI.
This value has been defined to give guidance on the applicable acceptance range for the difference in T_{max} because no value is defined in the guideline on the investigation of bioequivalence.

Due to the lack of a pre-defined limit, it was expected that for drugs where the onset of action is clinically relevant, T_{max} in the test and the reference product would occur at the same sampling time or in an adjacent one.
The definition of 20% as acceptance range intends not to reject products where T_{max} is not excessively rapid and the sampling time around T_{max} is very frequent. For example, if samples are taken every 5 minutes around T_{max} and T_{max} occurs after 2 h, a 10-minute difference in a non-adjacent sampling time is acceptable, but it would be rejected if the samples are required to be adjacent.

The 20% limit only defines arbitrarily what is considered as an apparent difference in T_{max}, in line with the wording of the guideline on the investigation of bioequivalence.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome

DE/H/6175/001-003	R	1.25	0.33-4.00	17
Ibuprofen Evolan (SE-National)	R	2.00	0.66-4.00	-38
Interstudy T_{max} Variability		**40%**		
MT/H/0166/000	S	2.00	0.50-4.00	-25
DE/H/6175/001-003	S	1.75	0.33-4.00	17
Ibuprofen Evolan (SE-National)	S	2.00	0.66-4.00	-38
Interstudy T_{max} Variability		**13%**		

- T_{max} (h) differences between reference products and test products that have been accepted, have varied (12 studies with PAR publicly available) range from -38% to +25%

It should be explained how the "≤ *20% difference in median*" specification was established. At present there has been no scientific rationale shared as to the basis for choosing ≤ 20% for the required difference acceptance criteria.

Proposed change:
T_{max} to be removed from the 'Main Pharmacokinetic Variables' within the newly proposed guidance but remains part of the 'Bioequivalence assessment' as 'comparable median and Range for T_{max}'.

Although the intra-subject and inter-subject variability affect the reliability or accuracy of the median T_{max} values obtained. The variability is not critical since the decision is based on medians and not based on 90% CI.

The fact that larger differences have been accepted in the past is not a valid reason to continue with an undefined acceptance range. T_{max} should be a primary PK endpoint because the onset is clinically relevant for analgesics. An acceptance range for T_{max} is necessary to avoid arbitrations.

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		Provide a clear explanation of the rationale behind a proposed '%' difference that can be effectively evaluated and modelled within statistically relevant parameters. Include an assessment as per general BE guidance detailed on p 15/27, 4.1.8 *"if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median T_{max} and its variability between test and reference product*".	
Ibuprofen oral use immediate release formulations 200 –800 mg product-specific bioequivalence guidance Line number 19	5	**Comment:** **It is stated in *Bioequivalence assessment: 90% confidence interval: Comparable median (≤ 20% difference) and range for T_{max}.*** More clarity is required how this difference will be calculated and compared. Is it mandatory to check the difference in ***range***? or only median will be suffice? Wilcoxon signed rank test will be adequate? Will study be concluded as NOT bioequivalent if there will be difference (>20%) in Median T_{max} and 90% CI of C_{max} and AUC is within 80.00 to 125.00? Does this require clinical correlation?	**Not accepted.** If the reference median T_{max} is at 1.5 h, 20% of 90 minutes is 18 minutes. Therefore, if the test product has a median of 1.75 h (i.e. 105 minutes), the difference of 15 minutes is acceptable. If T_{max} is expected after 30 minutes, samples every 5 minutes are required around T_{max}. The assessment of the range is more subjective. Only if differences are evident and worse for the test, it could be concluded that the products are not equivalent. The product will be concluded as NOT bioequivalent if there is a difference (> 20%) in Median T_{max} even if the 90% CI of C_{max} and AUC are within 80.00–125.00.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Does this impact in calculation of sample size? Meaning, sample size required to be calculated/justify based on this parameter as well?	As T_{max} is not assessed based on 90% CI, it is considered that the sample size does not have to be conducted based on T_{max}.
Bioequivalence assessment, Main PK variables (in the table)	6	**Comment:** PK parameter T_{max} is listed as one of the main PK variables (together with C_{max} and AUC_{0-t}). In our opinion, the inclusion of T_{max} in the primary endpoint analysis is not justified for ibuprofen and should be deleted. It is well known that PK parameter T_{max}: -is very sensitive parameter; -is highly variable and -has low statistical power. Furthermore, the sample size of bioequivalence study is not estimated to have enough statistical power for comparative T_{max} analysis. Thus, it is recommended to keep the requirements as presented in the guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**, that is the statistical evaluation of T_{max} should not be required unless rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events. This should be the case of special formulations with the claim of extremely rapid release (i.e. faster that the release of standard IR formulations) which is further claimed (with clinical studies) to be clinically relevant (i.e. faster onset of action in comparison to standard IR formulations). Thus, there is no need to require T_{max} as pivotal PK parameter in bioequivalence studies.	**Not accepted.** For the reasons explained by the stakeholder, T_{max} is assessed based on the difference between the medians of test and reference and the 90% CI is not required. However, for the assessment of the difference between median values of T_{max} an acceptance range has to be pre-defined to exclude apparent differences in T_{max} if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events. As T_{max} is not assessed based on 90% CI, it is considered that the sample size does not have to be conducted based on T_{max}.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Main pharmacokinetic variables: C_{max}, AUC_{0-t}	
Bioequivalence assessment, 90% confidence interval (in the table)	6	**Comment:** In this section, the comparable median (≤ 20% difference) and range for T_{max} is proposed. T_{max} is categorical variable that can only take values based on the planned sampling scheme. Expected values for T_{max} are consequently confined to some preselected categories and therefore, median T_{max} depends more on the study design and less on the formulation of the drug. Because median and not the average value is reported, T_{max} of only one subject can determine the position at which T_{max} will be. If we have active ingredient with T_{max} 0.5 hours post-dose, difference of more than 6 minutes already exceed 20%. In a case of T_{max} at 1 hour (ibuprofen), 20% occurs at difference of 12 minutes and in case of median T_{max} at 2 hours post-dose, 20% difference corresponds to 24 minutes. We can conclude that with normal sampling schedule the difference of median T_{max} for just one sampling time already exceeds 20%. Pharmacokinetic characteristics such as absorption rate are reported to vary between different formulations of ibuprofen, while apparent bioavailability is equivalent among the dosage forms. Shin et al. conducted PKPD study and compared two fast-acting ibuprofen formulations (ibuprofen arginine and solubilized ibuprofen capsule) with standard ibuprofen. Study	**Not accepted.** The sampling times should be defined in order to ensure that a difference larger than 20% can be discarded. T_{max} is expected to occur in the same sampling time for test and reference for drugs where the onset of action is clinically relevant. As the T_{max} of only one subject can determine the position at which T_{max} will be, the 20% (80–125%) acceptance range gives some flexibility and do not punish those studies with frequent sampling schedules. This example illustrates that different salt forms and dosage forms with median values of 0.42 and 0.5 can be considered equivalent with this 20% acceptance range. As the onset of action of these formulations is quicker than that of standard ibuprofen, it is adequate to conclude that the standard ibuprofen is not equivalent to more rapid formulations. The example provided by the stakeholder shows that the T_{max} differences had clinical relevance. More rapid pain relief and less re-medication was observed for the

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		provided information about their T_{max}: 0.42 hours for ibuprofen arginine, 0.5 hours for solubilized ibuprofen capsule and 1.25 hours for standard ibuprofen. A significant difference was observed between fast-acting formulations and standard ibuprofen for both – C_{max} and T_{max}. Furthermore, they concluded that different values of T_{max} and I_{max} (maximum inhibition) in the time course of COX2 inhibition did not have a major impact on the clinical efficacy or therapeutic end point (1). On the other hand, PKPD study comparing effervescent to standard ibuprofen provided information about mean T_{max} of effervescent ibuprofen to be 0.32 and mean T_{max} of standard ibuprofen to be 1.37 hours. Effervescent ibuprofen had also 60% higher C_{max}. This caused more rapid pain relief and less remedication for the effervescent formulation compared with standard ibuprofen (2). If we conclude, different formulations of ibuprofen (different salts) and different pharmaceutical forms (tablets, effervescent tablets, solubilized ibuprofen capsules …) of ibuprofen have their own PK characteristic (different T_{max} and C_{max}, but comparable bioavailability) and therefore, ibuprofen products should be treated individually case-by-case. Furthermore, because there are contradictory data about the influence of T_{max} on onset of action of ibuprofen, further investigations with clinical studies should be made to prove the correlation between these two parameters. Moreover, even when the correlation between T_{max} and onset of action would be shown in clinical studies, it would not make sense to limit T_{max} in the direction of smaller values, since	effervescent formulation compared with standard ibuprofen (2). For fast onset of action, the drug should be taken on empty stomach. Therefore, the SmPC recognises that the T_{max} difference caused by the food intake is clinically relevant in the case of ibuprofen.

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		these values would provide a faster onset of action of analgesics, i.e. a faster analgesic effect. According to SmPCs of different ibuprofen products, recommendations on the administration of ibuprofen with regard to food intake vary. If we sum up all the suggestions, the drug can be taken without regard to food, but should preferably be taken with or after meal with plenty of water. Patients with sensitive stomach should take ibuprofen together with food. Administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach, but total bioavailability is not markedly affected. Although the SmPCs of different ibuprofen IR products recommend taking it with food, some of them also contain recommendation that for fast onset of action, the drug should be taken on empty stomach. The magnitude of the food effect on the pharmacokinetics of ibuprofen was further investigated in literature. Food does not affect bioavailability as measured by the AUC but it reduces C_{max} and considerably affects T_{max}. Listed data are supported by results of studies: T_{max} values of fasting and fed state in the first study were 0.57 and 1.09 hours with difference 0.52 hours (91.2%), and in the second study 2.98 and 4.69 hours, with difference 1.71 hours (57.5%) (3, 4). Delay in T_{max} was for factor 1.91 and 1.58. In the first study C_{max} was reduced for 52.5% and in the second study for 35.2 %. This corresponds to data that ibuprofen fed T_{max} is 1.30 to 2.80	A 20% (80–125%) acceptance range has been defined only for the medians without 90% CI to ensure that T_{max} is not apparently different and the onset of action is equivalent. In this comparison it is necessary to take into account that C_{max} is assessed by means of 90% CI and T_{max} is not. Even if C_{max} was less affected than T_{max}, the boundaries of the 90% CI of C_{max} provide a larger difference than the ratio.

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		times longer than fasting, fed C_{max} is only 44-85% of fasted C_{max}, and to results from Hens et al, calculating T_{max} ratio in their study to be 1.67 (5, 6). Although there are recommendations in some of the ibuprofen's SmPC for taking ibuprofen products under fasting conditions when rapid onset of action is needed, the most SmPCs suggest taking ibuprofen with of after a meal. The large differences in the fasting and fed pharmacokinetics in case of ibuprofen products, which should preferably be taken with food, with values of 57.5% or even 91.2%, indicate that up to 20% allowed difference on the median T_{max} is clinically unfounded and too strict. Many factors influence the in vivo performance of orally administered drugs and dosage forms (7). Physiological factors that lead to variability in drug absorption and are of high importance can be the volume and the pH value of residual gastric contents, the motility of the stomach, the kinetic of gastric emptying of the co-administered water and the transit time of the drug product (8). Ibuprofen is highly permeable drug and shows no limits in dissolving at the neutral pH of small intestine (BCS class 2a drug). Variability in its systemic outcome is caused by differences in drug release and dissolution of the drug along the entire gastrointestinal tract. Therefore, the main factors contributing to variability are alternating motility patterns and alternating buffer capacity and pH changes along the GI tract, which are highly variable.	The recommendation to take ibuprofen with food is due to adverse gastrointestinal effects. But it is unquestionable that food affects the onset of action. To avoid the influence of external factors the studies are standardised and cross-over. See response to previous comments for the response to the fact that even one subject can be the reason, why it comes to the differences in median T_{max} between test and reference formulation.

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		In bioequivalence studies in fasting conditions, drug is administered randomly relative to motility cycle and, therefore, we introduce this random variable, independed of dosage form, into classic bioequivalence studies (6). Ibuprofen will remain in the stomach for unknown length of time and further, when it enters small intestine, the pH conditions in duodenum and jejunum must exceed pKa of ibuprofen (4,85) in order to its complete dissolution and absorption. pH along the gastrointestinal tract is a dynamic physiological variable and can take wide range of values. Therefore, T_{max} can significantly differ within and between subjects even under highly standardized conditions and even one subject can be the reason, why it comes to the differences in median T_{max} between test and reference formulation. **Proposed change:** In the table, section 'Bioequivalence assessment', modify text as to following: 90% confidence interval: 80.00 – 125.00 % for AUC_{0-t} and C_{max}. Statistical evaluation of T_{max} is not required unless applicable in the context of the application, e.g. in case of special formulations with the claim of extremely rapid release (i.e. faster that the release of standard IR formulations) which is further claimed to be clinically relevant (i.e. faster onset of action in comparison to standard IR formulations). In that case, comparison of T_{max} should be based on non-parametric methods and should be applied to untransformed data. In case of standard IR formulations, only T_{max} range should be comparable.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		References: 1. Shin D, Lee SJ, Ha YM, Choi YS, Kim JW, Park SR, Park MK. Pharmacokinetic and pharmacodynamic evaluation according to absorption differences in three formulations of ibuprofen. Drug Des Devel Ther. 2017 Jan 4;11:135-141. 2. Li H, Mandema J, Wada R et al. Modeling the onset and offset of dental pain relief by ibuprofen. J. Clin. Pharmacol. 2012; 52:89-101 3. Koenigsknecht MJ, Baker JR, Wen B, Frances A, Zhang H, Yu A, et al. In vivo dissolution and systemic absorption of immediate release ibuprofen in human gastrointestinal tract under fed and fasted conditions. Mol Pharm. 2017; 14(12):4295-304. 4. https://www.accessdata.fda.gov/drugsatfda_docs/anda/98/74-937_Ibuprofen_bioeqr.pdf accessed: 7. 6. 2022 5. Moore RA, Derry S, Wiffen PJ, Straube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs - a systematic review. Br J Clin Pharmacol. 2015; 80(3):381-8. 6. Hens B, Tsume Y, Bermejo M, Paixao P, Koenigsknecht MJ, Baker JR, et al. Low buffer capacity and alternating motility along the human gastrointestinal tract: Implications for in vivo dissolution and absorption of ionizable drugs. Mol Pharm. 2017; 14(12):4281-94. 7. Grimm M, Scholz E, Koziolek M, Kühn JP, Weitschies W. Gastric water emptying under fed state clinical trial conditions is as fast as under fasted conditions. Molecular Pharmaceutics. 2017; 14(12):4262-4271. 8. Grimm M, Koziolek M, Kuhn JP, Weitschies W. Interindividual and intraindividual variability of fasted state gastric fluid volume and gastric emptying of water. Eur J Pharm Biopharm. 2018; 127:309-17.	
Table Requirements	7	**Comment:** The draft guidance EMA/CHMP/356876/2017 Rev.1* is introducing a proposal for assessment of comparability of main	**Partly accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
for bioequivalence demonstration (PKWP)/ Bioequivalence assessment		additional pharmacokinetic variable T_{max}. More specifically, apart from the previously implemented requirement for a 'comparable median and range for T_{max}', newly, comparable median for T_{max} is to be concluded only if the difference between the test and reference median is less than or equal to 20%. While the motivation of PKWP to introduce acceptance criteria for T_{max} to conclude similarity in biopharmaceutical quality for generic medicines is understood, the current proposal is considered not acceptable for statistical and ethical reasons, as described in details in the below paragraphs. In line with the current version of EMA bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1/Corr), the sampling schedule should include frequent sampling around predicted T_{max} to provide a reliable estimate of peak exposure. However, the proposed 20% difference may easily lead to conclusion of non-comparability between formulations $T_{max(es)}$ even in cases where the calculated medians differ just by one sampling interval. For instance, in a study with sampling intervals of every 20 minutes, median achieved at 1.67 hours and 1.33 hours for test and reference, respectively, represents a difference of 26% (expressed as percentage of reference median, i.e. 100 × (1.67-1.33)/1.33 [%]). The situation becomes even more difficult for molecules with a shorter T_{max}, such as fast dissolving ibuprofens or paracetamol-containing products, where typically sampling intervals are more extensive in the first hour following the dosing. Here, sampling intervals of every 10 minutes for a product with an expected median of 0.5 hour means that a median difference in one	The sampling times should be defined based on the expected T_{max} of the reference product. If it is 45 minutes, samples every 5 minutes should have been defined. For example, at 0.17, 0.33, 0.5, 0.58, 0.67, 0.75, 0.83, 0.92, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sampling interval grossly fails the 20% acceptance criterion (observed difference would equal to 33%). Obviously, with median of 0.5 hour, one would have to sample at least every 6 minutes to satisfy the 20% difference. This would lead to extensive sampling intervals in the first hour after dosing (= 12 samples), since equidistant sampling intervals are typically required to achieve similar precision of C_{max} capture for majority of subjects. Not surprisingly, this is considered unrealistic due to the need of additional samples to describe the entire PK profile, logistical issues, but more importantly, due to excessive and unnecessary subject burden. Finally, there is no reasonable way of designing the study to decrease the sponsor risk or, increase power to pass this criterion, as it is feasible for other PK metrics such as C_{max} or AUC. The above examples are not only theoretical, but are based on real studies conducted by members of the association. A representative example is summarized in the following paragraph; the study was conducted in a well-established CRO located in Canada (data available on request). A randomized, 2-period, 2-sequence, single-dose, cross-over bioequivalence study under fasting conditions in 26 volunteers was designed for a generic formulation containing 500 mg of paracetamol; sampling intervals were employed as following: (0-hour) and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. The resulting test-to-reference ratios along with the 90% confidence intervals for C_{max} and $AUC_{(0-t)}$ were as following:	If the proposed 20% criterion is not satisfied, the products are considered as not similar enough and onset of action may differ.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		101.02 (91.69 - 111.31) and 100.80 (97.68 - 104.03), respectively. With respect to T_{max}, the test formulation displayed a median of 0.50 hours (min-max: 0.33-2.00 hours) and the reference displayed a median of 0.75 hours (min-max: 0.33-3.00 hours). The calculated medians from this study do not satisfy the proposed 20% criterion (difference of 33%) and thus might appear different, however, a statistical evaluation of within-subject (period) differences in T_{max} reveals otherwise (refer for details further below). In PK studies, concentrations are only taken typically at a set of predetermined times, and so T_{max} is an inherently discrete random variable (Patterson & Jones, 2006). While T_{max} is continuous in theory (Willavize et al., 2008), its distribution, either on the original scale (or on the log-scale), rarely follows a normal distribution (Chow & Liu, 2009). Consequently, statistical analysis of discrete variables like T_{max} requires the use of non-parametric (distribution-free) procedure. In fact, non-parametric analysis was implemented in the earlier version of the EM(E)A bioequivalence guideline and is still applicable as per the current WHO guideline (WHO, 2017). Construction of non-parametric confidence interval in 2x2 cross-over designs is based on period differences (Hauschke et al., 1990). For the above study with paracetamol, the treatment difference (Hodges-Lehmann estimate) was –0.125 hours (–7.5 minutes) along with 90%-confidence intervals (exact) ranging from –0.245 to 0.000 hours. The analysis detected no significant differences between test and reference	Based on the present Guideline on the Investigation of Bioequivalence the rapid release when onset of action is clinically relevant has to be assessed based on median T_{max} values. We cannot change the requirements of the guideline in this PSBGL but do clarify the acceptance range. While the Hodges-Lehmann estimator is an adequate estimator to compare T_{max} of Test (generic) and Reference (innovator) products, it estimates the median difference as compared to the current approach of comparable median and range for T_{max} which estimates the difference in medians. The current approach has been a requirement of the ibuprofen product-specific guideline since 2018 and the present revision of the guideline concerns better defining what is meant by comparable and not introducing a new method particularly one for which EMA experience in regulatory submissions is limited. Therefore, the continued use of the current approach is supported.

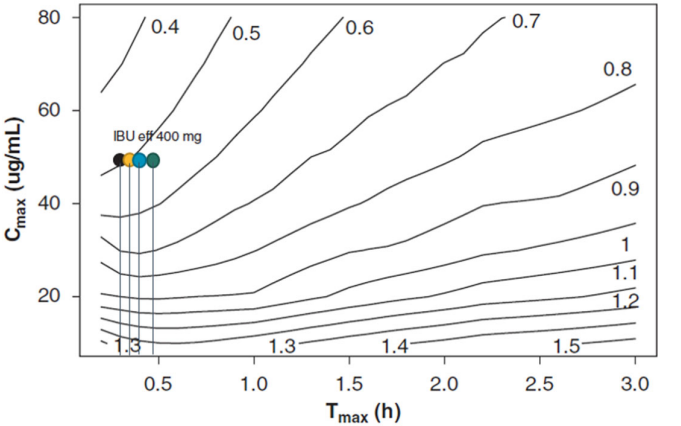
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(p=0.2234 for Wilcoxon-Mann-Whitney test; confidence interval includes zero). Clearly, this example illustrates that the newly proposed criterion concludes a difference where there is none based on statistical analysis appropriate for a discrete variable (and study design). Of note, the use of non-parametric analysis for T_{max} is not against general principles of the EMA bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1/Corr); non-parametric analysis is stated as not acceptable for analysis of PK parameters that are analysed following logarithmic transformation, i.e., applies to C_{max}, $AUC_{(0-t)}$ and/or $AUC_{(0-inf)}$. The difficulty in application of the new criterion may further be demonstrated by means of Monte Carlo simulation (e.g., by utilizing the sample function in R-software, R Core team, 2022). In this exercise, 26 values (sample size of the paracetamol study) were randomly sampled from population to obtain two sets of T_{max} values, one for test and one for reference. The population to sample from (for both products) exactly matched the T_{max} distribution observed in reality for the reference product in the above paracetamol study. For each of the 100'000 simulation runs, the test and reference medians along with their percent difference was computed and proportion of studies passing the 20% difference was evaluated. The results revealed that only 50% of simulated studies passed the proposed criterion of less than or equal to 20% difference despite the fact that population medians for both products were absolutely identical. Based on real data, this simulation demonstrates that power of the newly	The fact that the 90% CI includes the zero is not considered supportive. It may be simply due to a large variability and a small samples size. It is agreed that the proposed approach is not able to preserve the type 1 error. A larger sample size may be necessary. At least the present approach does not require that the complete non-parametric 90% confidence interval is contained within the 80–120% acceptance range. Only the difference between medians should be within the 20% (80–125%) limits.

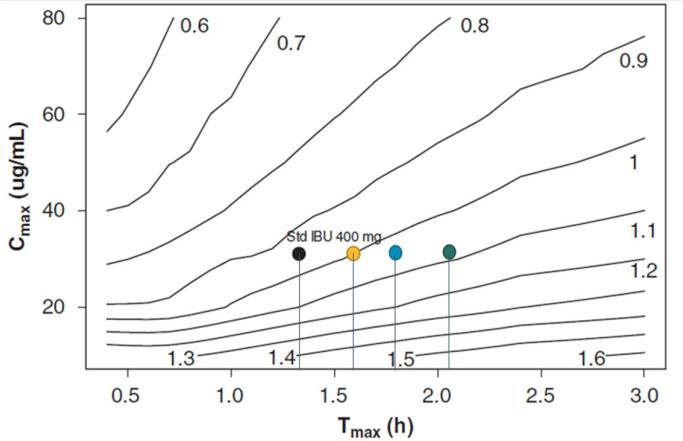
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		proposed acceptance criterion is low. Moreover, being a decision procedure based on point estimate only, it is not likely that the type I error is adequately controlled. Concerning assessment of 'comparable range' for T_{max}, in the past, draft product-specific bioequivalence guidance(s) for paracetamol, ibuprofen, tadalafil or dimethylfumarate were commented by stakeholders in the sense that it is not clearly defined and it is questionable how it should be practically evaluated. Unfortunately, these comments were not adequately addressed by PKWP, moreover, newly proposed PSBG revisions maintain the same uncertainty. Since objective rules when 'simply the numerical comparison' (the term used by PKWP in overview of comments EMA/CHMP/644909/2017) would or would not conclude similarity are lacking, unclear acceptance criterion referred to as 'comparable' has no place in a modern guidance. As stated by the PKWP in the response to stakeholder comments (EMA/CHMP/729976/2017), *'the use of T_{max} as pivotal variable is only applicable in certain situations. Unless the rate of absorption is important with regard to for instance efficacy, statistical evaluation of T_{max} is not required.'* Accordingly, this shall be implemented in the revised guidance text. Another important aspect to consider is that a definition on the importance and acceptable difference in T_{max} is not possible at the active substance level. There are several types of	See response to previous comments. The sponsor should define the sampling times with enough frequency to ensure that a difference higher than 20% can be discarded. The protocol should predefine the methodology by simply considering the difference between medians. This approach is based on the present requirements of the guideline on the investigation of bioequivalence, since the PSBGL cannot define different approaches. The rate of absorption is considered relevant for onset for action of ibuprofen. Therefore, as stated the T_{max} is not assessed with a statistical approach based on non-parametric 90% CI, but only with medians. 20% has been defined arbitrarily in the same way that 20% is used by default for C_{max} and AUC of all drugs, except HVDP and NTID.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ibuprofen-based products on the market: some have rapid action claims, other do not and there are several pharmaceutical forms. Several different chemical forms of the product (for example, salts or acid) are also available. This means that product-based granularity is required when assessing the relevancy of T_{max} differences and it is not reasonable to make a single general recommendation that is adequate for all types of immediate release ibuprofen products. **Proposed change:** In the table, section 'Bioequivalence assessment', modify text as to following: 90% confidence interval: 80.00 – 125.00% for AUC_{0-t} and C_{max}. Statistical evaluation of T_{max} is not required unless applicable in the context of the application, e.g. if rapid release is claimed to be clinically relevant. In that case, comparison of T_{max} should be based on non-parametric methods and should be applied to untransformed data. **References:** • CMDh minutes, EMA/CMDh/89802/2022 • EMA guideline, CPMP/EWP/QWP/1401/98 Rev.1/Corr • Hauschke D et al. (1990). Int J Clin Pharmacol Ther Toxicol. 28(2): 72-8 • Chow SC & Liu JP (2009). 3rd edition, Chapman & Hall/CRC, Boca Raton • Overview of comments, EMA/CHMP/644909/2017 & EMA/CHMP/729976/2017 • Patterson S & Jones B (2006). Chapman & Hall/CRC, Boca Raton	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• R Core team (2022). R Foundation for Statistical Computing, Vienna, Austria • WHO (2017). WHO Technical Report Series, No. 1003, Annex 6 • Willavize SA & Morgenthien EA. (2008). Pharm Stat. 7(1): 9-19	
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	8	**Comment:** We believe that 20% limit of acceptance for median T_{max} is unnecessarily restrictive and lack clinical justification and therefore that the current amendment to the guideline is not warranted at this time. A literature search has highlighted a number of insightful publications on the pharmacokinetics (PK) /pharmacodynamics (PD) relationship of ibuprofen.[123] A state of the art modelling and simulation methods were used in the paper by Li et al (2011) to describe the PK of ibuprofen administered as standard as well as effervescent formulation and to characterize the PKPD relationship between exposure and various PD endpoints of dental pain relief. PKPD models were developed for pain relief score, time to first perceptible relief (TFPR), time to meaningful pain relief (TMPR) and time to remedication (REMD). All PKPD models described by Li et al are of good quality, characterize well the PK and PKPD relationship of ibuprofen and dental pain relief across all PD endpoints and are suitable to explore what would be relevant acceptance criteria for T_{max} in the context provided by the bioequivalence guidance.	**Not accepted.** The arbitrary acceptance range of the 90% CI for the ratio test /reference of the primary PK parameters should ensure that PD differences are not detectable. The 20% (80–125%) acceptance range was defined for C_{max} and AUC because clinicians considered that those differences cannot be detected clinically. In this comment, a 20% difference in T_{max} is claimed to correspond to a detected difference of less than 6 or 12 minutes in the time to meaningful pain relief. Therefore, it is necessary to define an acceptance range that does not produce a clinically relevant time to meaningful pain relief.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Using the developed PK and PKPD models, simulations were performed by Li et al to build nomograms meeting targeted C_{max} and T_{max} combinations for both standard and effervescent ibuprofen formulations. Figure 1 and Figure 2 display the nomograms of TMPR for the effervescent and standard ibuprofen formulations respectively. The nomograms were used to evaluate changes in TMPR at increasing T_{max} values starting from the typical C_{max} and T_{max} reported by the paper (black circle). Scenarios reflecting a 20 (yellow circle), 30 (light blue circle) and 50% (green circle) increase in T_{max} are presented for both effervescent and standard formulations. For the purposes of this exercise C_{max} was assumed to remain constant. For the effervescent formulation (with a median T_{max} of 0.32 hours), a 20, 30 and to 50% increase results in T_{max} of 0.38, 0.42 and 0.48 hours, respectively. Such an increase translates into a corresponding TMPR increase of less than 6 minutes across all scenarios (median TMPR remains between 0.5 and 0.6 hours). For the standard ibuprofen (with a median T_{max} of 1.37 hours), a 20, 30 and 50% increase results in T_{max} of 1.64, 1.78 and 2.05 hours respectively. Such an increase translates into a corresponding TMPR increase of less than 12 minutes across all scenarios (median TMPR remains between 0.9 and 1.1h).	

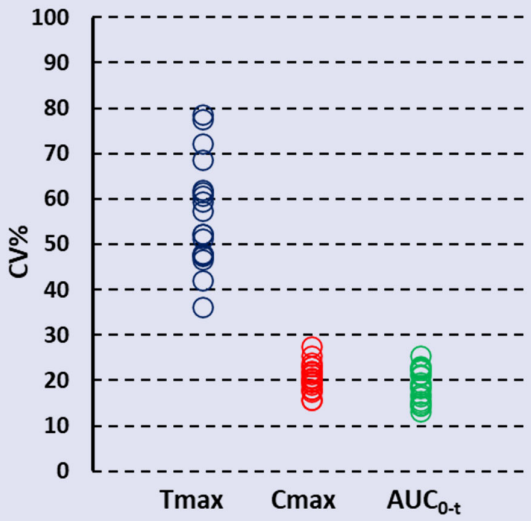
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		TMPR is used as a graphical example in this report, but similar considerations can be applied for TFPR and REMD. Less of an impact would be observable for TFPR with changes in median TFPR of less than 3 minutes for both effervescent (median TFPR between 0.25 and 0.3h) and standard (median TFPR between 0.5 and 0.55h) formulations assuming same % changes in T_{max} as presented for TMPR. **Figure 1 TMPR nomogram for ibuprofen formulations. Curves represent median TMPR (hour). Solid dots represent predicted TMPR values for ibuprofen effervescent**  *Adapted from Figure 9 by Li et al. The black circle represents typical parameters for the effervescent ibuprofen formulation while yellow, light blue and green circles represent 20, 30 and 50% increase in T_{max}.*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Figure 2 TMPR nomogram for ibuprofen formulations. Curves represent median TMPR (hour). Solid dots represent predicted TMPR values for standard ibuprofen  *Adapted from Figure 9 by Li et al. The black circle represents typical parameters for the standard ibuprofen formulation while yellow, light blue and green circles represent 20, 30 and 50% increase in T_{max}.* Based on the results presented above, a 20% change in T_{max} does not appear to translate into a clinically meaningful change on any of the key efficacy endpoints for dental pain relief with increase in median TFPR and TMPR of less than 6 minutes and REMD of less than 5% for both standard and effervescent ibuprofen formulations. However, changes in T_{max} up to 50% still result in highly comparable clinical responses across the various PD endpoints.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This lack of meaningful impact of change in T_{max} was also highlighted by the work of Troconiz et. al (2000) and Cristofoletti and Dressman (2014) who found respectively that maximum antipyretic effect was similar and occurred at the same time for two formulations of Ibuprofen with a 1 hour difference in T_{max} (i.e., a 50% difference)[1] and that a 2.2 hour delay in T_{max} only translates into a 30 mins delay in the onset of dental pain relief and no difference in maximum efficacy.[2] Overall the clear interpretation of findings from all these studies is that, even in the case where the T_{max} of Test and Reference products differ by 50%, this difference would not be expected to have a significant impact on factors such as time to maximum antipyretic efficacy or time to onset of analgesia as well as maximum efficacy. Therefore, we believe that A 20% limit of acceptance for median T_{max} is thus unnecessarily strict and lack clinical justification. A wider T_{max} acceptance range is supported, ensuring bioequivalence, maintaining adequate efficacious response. References: 1- Trocóniz IF et al. Clinical pharmacokinetics. 2000 Jun;38(6):505-18. 2- Cristofoletti R & Dressman JB. Journal of Pharmaceutical Sciences. 2014 Oct 1;103(10):3263-75. 3- Li H et al. J Clin Pharmacol. 2012 Jan;52(1):89-101	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: We are not supportive of the currently proposed criteria for all the reasons outlined in our response. However, in the case where reverting to current guideline wouldn't be an acceptable option we would be happy to discuss as part of a scientific discussion a possible alternatives such as applying a wider criterion based on clinical meaningfulness determined by scientific data (clinical and/or model).	
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	8	**Comment:** Because of the high variability of T_{max} we believe that 20% limit of acceptance for median T_{max} will make very difficult for sponsors to design and predict the outcome of bioequivalence studies that will allow the demonstration of bioequivalence between reference and test products. We believe this is in opposition to the spirit of the product specific bioequivalence guidelines whose aim is to facilitate study design and better predictability during the authorisation process.". A publication from Andrew Moore et al. (2014) report the median T_{max} for different format of Ibuprofen. For the "faster" forms of ibuprofen such as ibuprofen arginate, ibuprofen lysinate or sodium ibuprofen dihydrate, the absorption rate is high with a T_{max} at around 30 min (between 29–35 minutes).1 Applying a threshold of 20% implies that a median change of more than 6 minutes in T_{max} would lead to concluding inequivalence even if C_{max} and AUC ratios are within the acceptance range.	**Not accepted.** The objective of the PSBGL is to clarify the regulatory requirements to facilitate study design and better predictability during the authorisation process, but it is not to facilitate the predictability of the study outcome. To exclude differences between medians of 20% of T_{max} when the reference product exhibits a quick absorption rate it is necessary to take more frequent samples around expected T_{max} of the reference product (e.g. every 5 minutes). In standard ibuprofen formulations, samples should be taken every 15 minutes, which is the usual sampling frequency. The impact of the large variability is limited by the use of the median values, instead of the 90% CI. The reference product should be selected based on the similarity of the rate of absorption, not based on the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		For standard ibuprofen formulations, with T_{max} occurring at approximately 90 minutes1, the 20% difference represents a median change of 18 minutes. Additionally, the publication also highlights the high variability of Tmax parameter as the mean T_{max} for standard Ibuprofen reported in the different studies assessed by the authors are spread across a range that goes from 31 to 180min (more than 5-fold difference). The coefficient of variation expressed in Percentage (CV%) is another parameter that can be used to better understand the extent of variability for a specific metric in relation to the mean and it is the ratio of the standard deviation to the mean often expressed as a percentage. We retrieved and where unavailable calculated (using the formula: CV% = (Standard Deviation/Mean [T_{max} or C_{max} or AUC_{0-t}])*100) the values of CV% for 16 PK studies providing data for Standard Ibuprofen reported in the Moore publication. Across all the studies considered, the CV% for T_{max} was consistently higher between studies compared to that of C_{max} and AUC_{0-t} as presented in Figure 1.	width of the acceptance range. If the test product is more quickly absorbed, the selection of a slower reference product will make the study fail even if the acceptance range is wider. It may be correct that the demonstration of equivalence will be more difficult for more quickly absorbed reference products, and less quickly absorbed generics will be developed more easily, but the risk of re-medication will be the same as for the corresponding reference medicinal product. The acceptance ranges of a bioequivalence study for a generic product are not defined based on M&S. The use of clinical data to support the therapeutic equivalence of the applied product should be submitted as a hybrid application.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Figure 1: Coefficient of variation (CV%) for Tmax, Cmax and AUC_{0-t} observed in 16 different studies reporting the pharmacokinetic profile for Standard Ibuprofen (n=19). The selection of studies is based on the studies discussed in Moore et al. 2014. ***References:*** *Internal Reckitt studies:* *NL0309, NL0405, NL0601, NL0703, NL0810, NL9709, NL9720, NL9809, R07-1009.* *Studies from scientific literature:* *Ceppi Monti N. et al. Arzneimittelforschung. 1992 Apr;42(4):556-9; Gontarz N. et al. Clinical pharmacy. 1987 May 1;6(5):413-6; Lenhard G. et al. Arzneimittel-forschung. 1990 Dec 1;40(12):1358-62; Lockwood G. F., et al. Clinical Pharmacology & Therapeutics. 1983 Jul;34(1):97-103; Schettler T., et al. Clinical Drug Investigation. 2001 Jan;21(1):73-8; Sörgel F. et al. International Journal of Clinical Pharmacology & Therapeutics. 2005 Mar 1;43(3); Walter K. et al. Arzneimittel-forschung. 1995 Aug 1;45(8):886-90.* A reference product with a later T_{max} will have a wider acceptance range, for example, 20% of 60 min being ±12mins compared to 20% of 120 min being ±24 mins and may	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		therefore encourage a bias in selecting a slower acting reference that is not necessarily in the interest of the patient from a risk of re-medication. References: 1- Moore RA et al.. PAIN®. 2014 Jan 1;155(1):14-21. **Proposed change:** We are not supportive of the currently proposed criteria for all the reasons outlined in our response. However, in the case where reverting to current guideline wouldn't be an acceptable option we would be happy to discuss as part of a scientific discussion a possible alternatives such as applying an upper limit of median T_{max} determined by scientific data (clinical or model) after which a Test product would not be consider immediate release Ibuprofen?	
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	8	**Comment:** As discussed in our previous point T_{max} for Ibuprofen is highly variable and therefore study sponsors will likely have to make changes to their study design in order to increase their chance to meet the acceptance range of 20% difference in median T_{max}. Some of the most likely changes that we can foresee are: - An increase in the total number of subjects to try and compensate for the high degree of variability. - An increase in the number of blood draw using very tight sampling intervals in order to ensure that T_{max}, which is a continuous variable, is not missed.	**Not accepted.** As bioequivalence studies for ibuprofen are usually of cross-over design, the large variability between subjects is expected to have a negligible impact. It is not considered necessary to recruit more homogeneous population. Although T_{max} is more variable, as only the medians are compared the sample size is not expected to increase excessively.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- Increased need to recruit a homogeneous demographic, to reduce subject to subject variability, in an effort to achieve the very restrictive 20% difference. All these changes have specific pitfall: Increasing the number of subjects will increase unnecessary drug exposure in the absence of a documented safety or efficacy concern while increasing the number of blood draw could cause practical and ethical concern. Finally an homogenisation of the demographic of the subject might induce biases in the results and would go against the current type of approach supported by regulators encouraging for more diversity and inclusion.	It is expected only that more frequent sampling is needed to ensure that T_{max} occurs in the same sampling time or a sampling time that does not differ more than 20%. More frequent sampling will also help to characterise C_{max} better. Studies with up to 25 samples are frequent nowadays since bioanalytical methods do not need large volumes of blood.
Line 19 (table) Bioequivalence assessment Comparable median (≤ 20% difference) and range for T_{max}.	8	**Comment:** The regulatory framework has restrictions in place surrounding acceptable reference products this is isn't considered in the new criteria where this compares like with like. Both Ibuprofen salts and acids are included in the immediate release oral ibuprofen category. Eudralex Volume 2A states, "A generic product and a reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopoeia. Furthermore, Article 10(2)(b) of the amended Directive provides that the various immediate release oral forms, which would include tablets, capsules, oral solutions and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10."	**Not accepted.** Different salts and dosage forms can be considered as generics if bioequivalence is shown. It is not expected that the different salts and dosage forms have the same or similar T_{max}. As there are multiple reference medicinal products with different T_{max} values, the Applicant should select the reference medicinal product with the required T_{max}. There is no intention to move towards efficacy studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The immediate release oral ibuprofen category includes diverse formulations such as ibuprofen, arginine, lysine, sodium salts, solid dose and orodispersible tablets. There are many other immediate release formats included in this category and from a legal basis point of view they are considered the "same". The proposed new guidelines expects that all the formats should have a comparable T_{max}. Some consequences from the proposed criterion is limited development, reduced innovations and restricted consumer/ patient benefits. Generic applications meetings the proposed criterion could lead to unnecessary clinical and ethical burden due to multiple bioequivalence studies being required to meet the narrow window and a move towards efficacy studies.	The proposed criterion intends to ensure equivalent onset of action for the patients' benefit. Any innovation should prove to be equivalent or the claimed clinical advantage.