# IBUPROFEN BE GUIDELINE CONSULTATION 2022

**Reckitt position**

**Graham Pennick**
**Global Medical Science Lead – Analgesics**

# EMA general guidance on investigating BE

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE
*COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)*
*Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr*

Standard study design:
"If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended."

| | Period 1 | Period 2 |
|---|---|---|
| Group 1 n=x | Test product | Reference product |
| Group 2 n=x | Reference product | Test product |

In studies to determine bioequivalence after a single dose, AUC(0-t), AUC(0-∞), residual area, Cmax and tmax should be determined.

A statistical evaluation of tmax 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 tmax and its variability between test and reference product.

# EMA specific guidance on investigating BE

31 May 2018 EMA/CHMP/356876/2017 Committee for Medicinal Products for Human Use (CHMP) Ibuprofen oral use immediate release formulations 200 - 800 mg product-specific bioequivalence guidance

| | |
|---|---|
| **Bioequivalence assessment** | **Main pharmacokinetic variables:** $AUC_{0-t}$, $C_{max}$ and $T_{max}$. |
| | **90% confidence interval:** 80.00 – 125.00% for $AUC_{0-t}$ and $C_{max}$. Comparable median and range for $T_{max}$. |

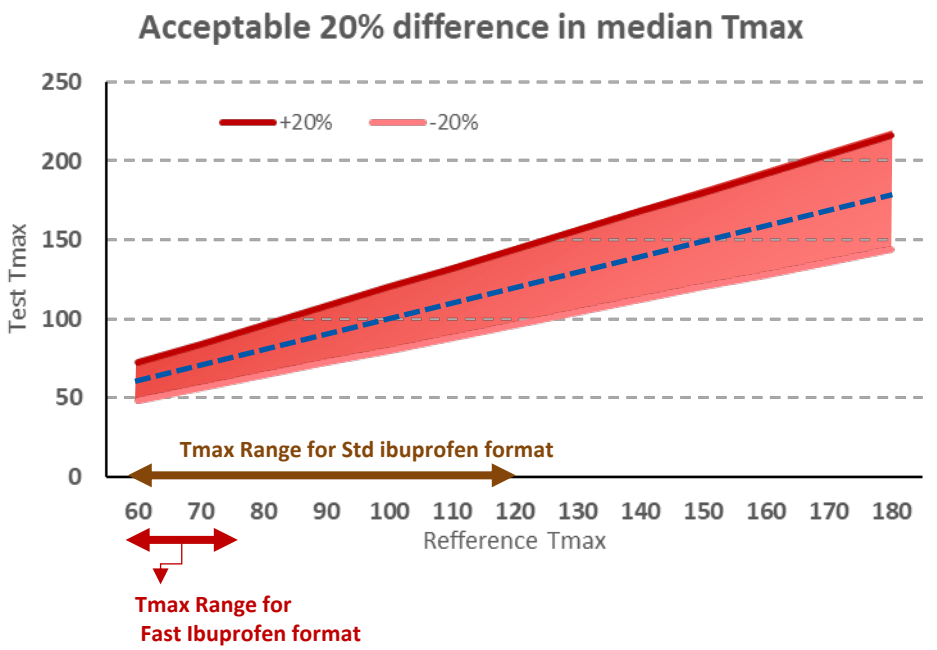
| | |
|---|---|
| **Bioequivalence assessment** | **Main pharmacokinetic variables:** $AUC_{0-t}$, $C_{max}$ and $T_{max}$. |
| | **90% confidence interval:** 80.00 – 125.00% for $AUC_{0-t}$ and $C_{max}$. Comparable median (≤ 20% difference) and range for $T_{max}$. |

- A public consultation on the proposed changes to the BE Guidance began on the **4th April 2022.**
- The consultation was open for **3 Months (closed 31st July).**
- It included, **Ibuprofen, Paracetamol** and **Tadalafil.**

# Acceptable Tmax ranges with 20% selectivity

Example Data for Standard Ibuprofen Table with arbitrary values for Median Tmax

| | Comparable Tmax Median for Test | | |
|---|---|---|---|
| | Tmax Median Test < Tmax Median Ref | | Tmax Median Test > Tmax Median Ref |
| Reference Median Tmax (min) | 20% difference | | 20% difference |
| 60 | 48 | | 72 |
| 70 | 56 | | 84 |
| 80 | 64 | | 96 |
| 90 | 72 | | 108 |
| 100 | 80 | | 120 |
| 110 | 88 | | 132 |
| 120 | 96 | | 144 |
| 130 | 104 | | 156 |
| 140 | 112 | | 168 |
| 150 | 120 | | 180 |
| 160 | 128 | | 192 |
| 170 | 136 | | 204 |
| 180 | 144 | | 216 |



# Feedback provided by Reckitt to the consultation

# General comments:

- Specific bioequivalence guidance, is to “facilitate transparent, predictable and scientifically robust assessment in future marketing authorisation procedures”*.

- The proposed additional requirement/restriction for Ibuprofen and Paracetamols does not seem to allow for a consistent approach to be taken across similar APIs, particularly within the NSAID family (*e.g. diclofenac, dexibuprofen, naproxen*). This could result in less scrutiny for products containing these APIs.

- Tmax should be evaluated 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, does not meet the criteria that requires Tmax to be evaluated. *(no data of any adverse events related to the rapid release of Ibuprofen from the formulation.)*

**according to the Concept paper on the development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013). ** according to* According to the “Guideline on the investigation of bioequivalence”, CPMP/EWP/QWP/1401/98 Rev.1/Corr**,

**Unnecessarily restrictive & lack clinical justification**

- Several insightful publications on the pharmacokinetics (PK) /pharmacodynamics (PD) relationship of ibuprofen.[123]

- Troconiz et. al (2000) and Cristofoletti and Dressman (2014) highlight a lack of meaningful impact of change in Tmax who found respectively:
  - Maximum antipyretic effect was similar and occurred at the same time for two formulations of Ibuprofen with a 1 hour difference in Tmax (i.e., a 50% difference)[1]
  - 2.2 hour delay in Tmax only translates into a 30 mins delay in the onset of dental pain relief and no difference in maximum efficacy.[2]

- 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.

*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*

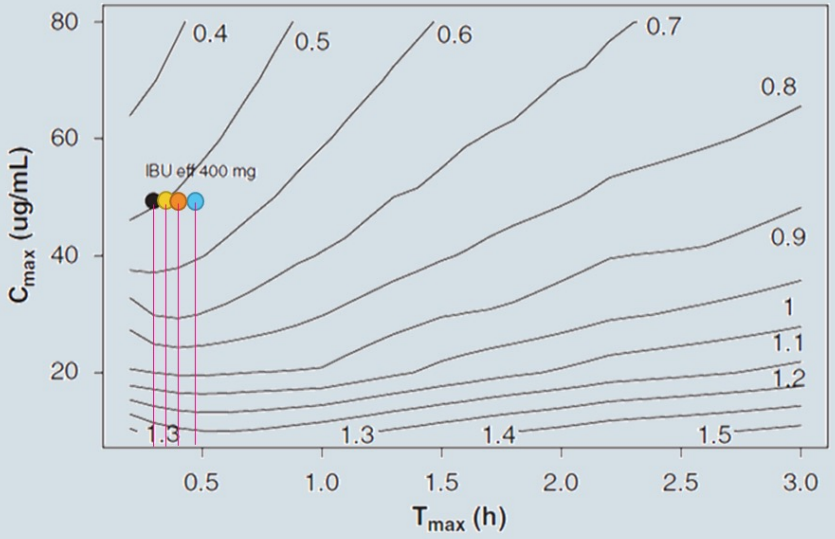
# TMPR simulations – Li et al. J Clin Pharmacol 2011

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).

**Fast Format**

**IBU eff 400 mg Tmax = 0.32h**

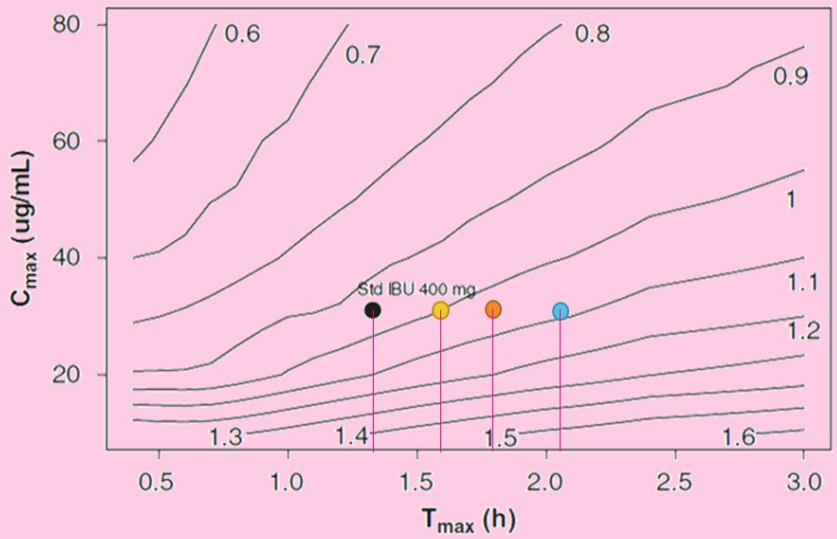
- 20, 30 and 50% increase result in Tmax of 0.38, 0.42 and 0.48h
- Assuming same Cmax, increase in Tmax results in TMPR changes of less than 6 minutes (between 0.5 and 0.6)




**Standard Format**

**IBU std 400 mg Tmax = 1.37h**

- 20, 30 and 50% increase result in Tmax of 1.64, 1.78 and 2.05h
- Assuming same Cmax, a 20% increase in Tmax is less than 6 minutes change in TMPR (between 0.9 and 1), less than 12 minutes for 50% increase



**Unnecessarily restrictive & lack clinical justification**

Overall the clear interpretation of findings from all these studies is that:

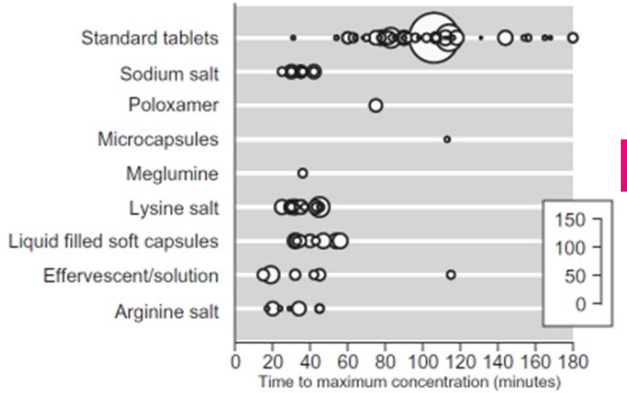
Even in the case where the Tmax of Test and Reference products differ by 50%, this difference would not be expected to have a significant impact on factors such as time to maximum antipyretic efficacy or time to onset of analgesia as well as maximum efficacy.

A 20% limit of acceptance for median Tmax is thus unnecessarily strict and lack clinical justification.

**Proposed change**: We are not supportive of proposed criteria. If reverting to current guideline is not an acceptable option we would be happy to discuss a possible alternatives such as applying a wider criterion based on clinical meaningfulness determined by scientific data (clinical and/or model)

# High variability of Tmax

- High variability of Tmax will make very difficult to design and predict the outcome of bioequivalence studies. In opposition to the spirit of the product specific BE guidelines whose aim is to facilitate study design and better predictability*.
- Moore et al. (2014) report the median Tmax for different format of Ibuprofen.
  - "faster" forms of ibuprofen (arginate, lysinate or sodium), Tmax around 30 min.[1] Change of more than 6 minutes would not be acceptable.
  - "standard" ibuprofen Tmax around 90 minutes[1]. Change of 18 minutes would not be acceptable.




*Adapted from Moore et al 2014*

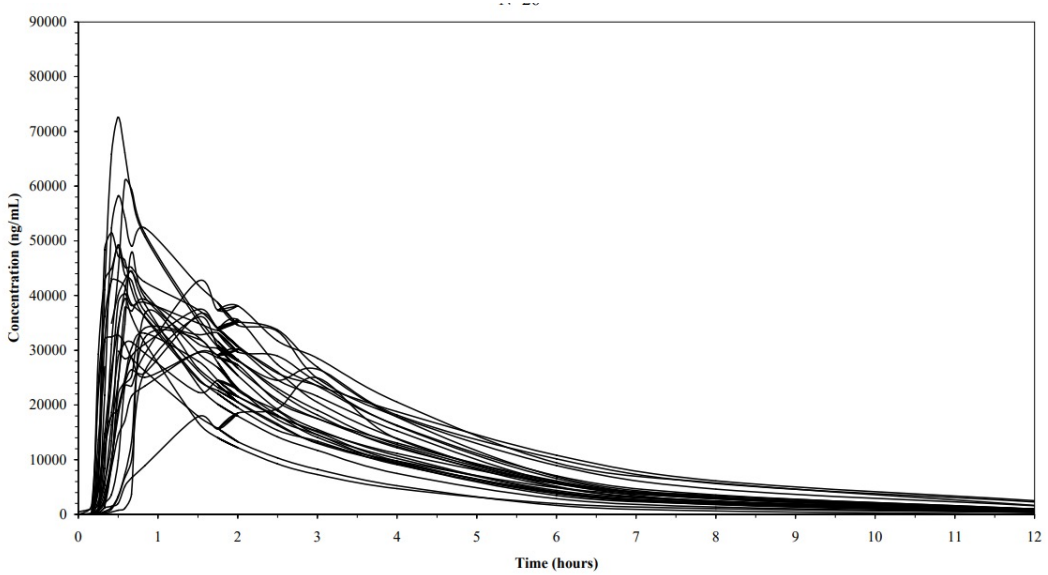
**Fig. 1.** Results for $T_{max}$ from individual studies. The size of the symbol is proportional to the number of subjects (inset scale).

High variability of Tmax.
Mean Tmax for standard Ibuprofen reported spread across 31 to 180min (more than 5-fold difference).

**according to the Concept paper on the development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013). 1- Moore RA et al.. PAIN®. 2014 Jan 1;155(1):14-21.*

# High variability of Tmax

- Coefficient of variation (CV%) can be used to better understand the extent of variability for a specific metric in relation to the mean.
- 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 Tmax was consistently higher between studies compared to that of Cmax and AUC0-t As presented below



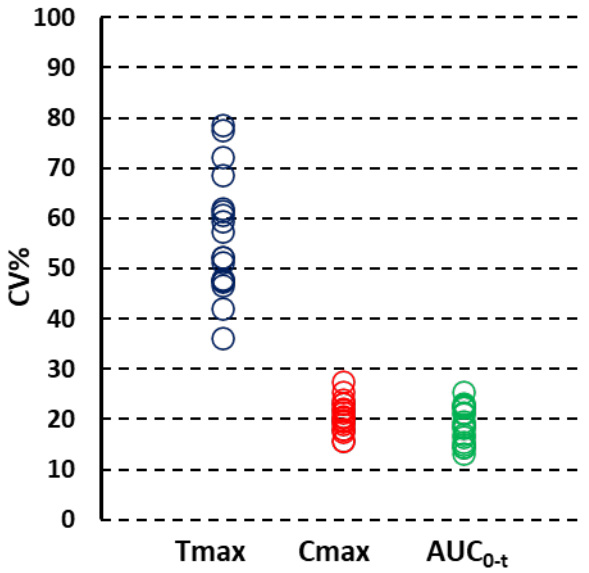




**Figure 1:** Coefficient of variation (CV%) for Tmax, Cmax and $AUC_{0-t}$ observed in 16 different studies reporting the pharmacokinetic profile for Standard Ibuprofen (n=19). The selection of studies is based on the studies discussed in Moore et al. 2014.

***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.*

# High variability of Tmax

- A reference product with a later Tmax 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 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.

**Proposed change:** We are not supportive of proposed criteria. If reverting to current guideline is not an acceptable option we would be happy to discuss a possible alternatives such as applying an upper limit of median Tmax determined by scientific data (clinical or model) after which a Test product would not be consider immediate release Ibuprofen?

# Potential issues with study design

- Tmax 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 Tmax. 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. (increase unnecessary drug exposure)
  - An increase in the number of blood draw using very tight sampling intervals in order to ensure that Tmax, which is a continuous variable, is not missed. (could cause practical and ethical concern)
  - Increased need to recruit a homogeneous demographic, to reduce subject to subject variability, in an effort to achieve the very restrictive 20% difference. (might induce biases in the results and would go against the current type of approach supported by regulators encouraging for more diversity and inclusion.)

# Regulatory framework

- The immediate release oral ibuprofen category includes diverse formulations such as ibuprofen, arginine, lysine, sodium salts, solid dose and orodispersible tablets and many other immediate release formats 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 Tmax.

- Some consequences from the proposed change
  - Limit development,
  - Reduced innovations
  - 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.

# Thank you for your attention

**Thank you to fellow Reckitt medical science team esp. Fred Esclassan & Toba Sanni**

**Thank you to Jean-Michel Cardot for his consultation and expert review**

# References

*Ceppi Monti N , Gazzaniga A, Gianesello V, Stroppolo F, Lodola E. Activity and pharmacokinetics of a new oral dosage form of soluble ibuprofen. Arzneimittel-forschung. 1992 Apr 1;42(4):556-9.*

*Cristofoletti R, Dressman JB. Use of physiologically based pharmacokinetic models coupled with pharmacodynamic models to assess the clinical relevance of current bioequivalence criteria for generic drug products containing ibuprofen. Journal of Pharmaceutical Sciences. 2014 Oct 1;103(10):3263-75.*

*Gontarz N, Small RE, Comstock TJ, Stalker DJ, Johnson SM, Willis HE. Effect of antacid suspension on the pharmacokinetics of ibuprofen. Clinical pharmacy. 1987 May 1;6(5):413-6.*

*Lenhard G, Kieferndorf U, Berner G, Engels B, Vögtle-Junkert U. Pharmakokinetik und Bioäquivalenz von zwei Ibuprofen-Formulierungen. Arzneimittel-Forschung. 1990;40(12):1358-62.*

*Li H, Mandema J, Wada R, Jayawardena S, Desjardins P, Doyle G, Kellstein D. Modeling the onset and offset of dental pain relief by ibuprofen. The Journal of Clinical Pharmacology. 2012 Jan;52(1):89-101.*

*Lockwood GF, Albert KS, Gillespie WR, Bole GG, Harkcom TM, Szpunar GJ, Wagner JG. Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. Clinical Pharmacology & Therapeutics. 1983 Jul;34(1):97-103.*

*Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. PAIN®. 2014 Jan 1;155(1):14-21.*

*Schettler T, Paris S, Pellett M, Kidner S, Wilkinson D. Comparative pharmacokinetics of two fast-dissolving oral ibuprofen formulations and a regular-release ibuprofen tablet in healthy volunteers. Clinical Drug Investigation. 2001 Jan;21(1):73-8.*

*Sörgel F, Fuhr U, Minic M, Siegmund M, Maares J, Jetter A, Kinzig-Schippers M, Tomalik-Scharte D, Szymanski J, Goeser T, Toex U. Pharmacokinetics of ibuprofen sodium dihydrate and gastrointestinal tolerability of short-term treatment with a novel, rapidly absorbed formulation. International Journal of Clinical Pharmacology & Therapeutics. 2005 Mar 1;43(3).*

*Trocóniz IF, Armenteros S, Planelles MV, Benítez J, Calvo R, Domínguez R. Pharmacokinetic-pharmacodynamic modelling of the antipyretic effect of two oral formulations of ibuprofen. Clinical pharmacokinetics. 2000 Jun;38(6):505-18.*

*Walter K, Weiss G, Laicher A, Stanislaus F. Pharmacokinetics of ibuprofen following a single administration of a suspension containing enteric-coated microcapsules. Arzneimittel-forschung. 1995 Aug 1;45(8):886-90.*

*Internal Reckitt studies: NL0309, NL0405, NL0601, NL0703, NL0810, NL9709, NL9720, NL9809, R07-1009.*

"Guideline on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev.1/Corr *Guideline o the Investigation of Bioequivalence (europa.eu)*

*Concept paper on the development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013). https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-product-specific-guidance-demonstration-bioequivalence_en.pdf*