COMMENTARY

The Impact of the EMA Change in Definition of "Dose" on the BCS Dose–Solubility Ratio: A Review of the Biowaiver Monographs

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ABSTRACT: The Biopharmaceutics Classification System (BCS) defines the solubility characteristics of an active pharmaceutical substance based on its dose–solubility ratio: for highly soluble drugs this ratio is less than 250 mL over a defined pH range. Prior to the revision of the European Medicines Agency (EMA, formerly EMEA) guideline in 2010, the "dose" in this ratio was consistently defined by the US FDA, the EMA, and the WHO biowaiver guidelines as the highest dosage strength. However, in the revised EMA guideline, the dose is defined as the highest single dose administered according to the Summary of Product Characteristics. The new EMA criterion for highly soluble may be closer to the actual conditions of use, but it is not in line with the dose that would be used in the *in vivo* bioequivalence study. This paper evaluates the impact on the BCS classification of the active pharmaceutical ingredients of the published biowaiver monographs and discusses the consequences of the possible change in classification on biowaiver recommendations. Using the current definition of dose by the EMA, the biowaiver recommendations for metoclopramide hydrochloride and verapamil hydrochloride are no longer valid according to EMA criteria. For prednisolone and prednisone, a reevaluation of the biowaiver recommendation, taking into account the usual dosing levels, seems appropriate. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:65–70, 2014
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INTRODUCTION

Since the introduction of the Biopharmaceutics Classification System (BCS),[1] most regulatory authorities have started to apply this system for bioequivalence guidance. The BCS is based on two important processes for the absorption of a drug substance, namely its solubility and hence ease of dissolution in the upper gastrointestinal tract and its permeation through the membrane. The BCS classifies the characteristics of these processes by categorizing these parameters as "high" or "low". The various regulatory authorities have somewhat different criteria for categorizing the solubility and permeability. The solubility of an active pharmaceutical ingredient (API) is in all cases defined by calculating the dose–solubility ratio (D/S) expressed by volume (mL), that is, the volume sufficient to dissolve the dose, but the dose and the range of conditions over which the solubility is determined may differ from jurisdiction to jurisdiction.

An important application of BCS in the regulatory documents is the use of BCS in the guidance for biowaiver procedures. One of the most important criteria for deciding whether a BCS-based biowaiver is appropriate is the BCS class of the API. For instance, products containing BCS class IV APIs are excluded from the BCS-based biowaiver procedure. Additionally, products containing class III APIs cannot, as of this writing, be approved in the USA by the biowaiver procedure. In the EU and countries using the WHO criteria, products containing Class III APIs are only eligible for biowaiving if they are very rapidly dissolving. Class II APIs are only eligible for the biowaiver procedure in countries using the WHO criteria and then only in the case of a weak acid that is highly soluble at pH 6.8. By contrast, Class I APIs are eligible for the biowaiver procedure in all jurisdictions that apply it (Japan, notably, is a country that does not yet allow approval of drug products using the BCS-based biowaiver procedure). In general, the regulatory authorities consider an API highly soluble if its D/S ratio is less than 250 mL.

The former European Medicines Agency guideline (EMA, formerly EMEA, 2001) and the present US FDA (2000) guidance define dose as the highest dosage strength marketed as an oral immediate release (IR) dosage form, that is, the tablet or capsule with the highest content of API.[2,3] However, the revised EMA (2010) guideline defines dose as the highest single oral IR dose recommended for administration in the Summary of Product Characteristics (also known as the Prescribers' Information).[4] The WHO has a more flexible definition. If the API appears on the WHO Model List of Essential Medicines (EML), the highest dose recommended in that list is to be applied for D/S ratio calculation. For APIs not on the EML, the highest dosage strength available on the market as an oral solid dosage form is used.[5]

As the BCS classification is an important parameter for biowaiver eligibility, it is important to unambiguously understand how the D/S ratio is calculated. To demonstrate the differences that can arise as a result of the differences in definition of dose, we evaluated its impact on the BCS classification of the APIs for which biowaiver monographs had been published up to 2011 (in this Journal and on the FIP website www.fip.org/bcs). This article identifies changes in BCS classification for this set

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of APIs and discusses the impact of the change on the API's eligibility for the BCS-based biowaiver. The results are also addressed in the context of patient use and in the framework of other regulations relating to bioequivalence.

METHODS

The impact of the change in definition of D on the D/S ratio and hence the BCS classification was evaluated for the 27 APIs for which a biowaiver monograph had been published up to June 2011. The highest single dose administered as an IR oral drug product was obtained from Summaries of Product Characteristics (SmPCs) on the website of the Dutch Medicines Evaluation Board and Martindale Extra Pharmacopoeia. Where no SmPC was available from the Dutch Medicines Evaluation Board, the SmPC as published on the company's website was taken and compared with the Martindale information. The solubility value S was taken from the respective biowaiver monographs: to evaluate whether the D/S met the solubility criterion, the worst-case solubility values were used, that is, the lowest value in the pH range 1–6.8, the range applied by the EMA. With these values for solubility and dose, the "new" worst-case D/S ratios were calculated for each active substance.

RESULTS AND DISCUSSION

Figure 1 summarizes the results for all APIs evaluated. Table 1 lists the 24 APIs for which the D/S ratio was recalculated. As the authors of the biowaiver monographs for lamivudine, levofloxacin, and metronidazole had already taken the different dose definition into the calculation of D/S into consideration, results for these three APIs are not tabulated.

For acyclovir, atenolol, cimetidine, ciprofloxacin, furosemide, ibuprofen, lamivudine, levofloxacin, and ranitidine, the highest single dose recommended for administration in the SmPC is equal to the highest dosage strength available, so for these drugs, the BCS classification and hence the biowaiver recommendation is not altered.[6–14] The solubility values for acetaminophen (paracetamol), chloroquine salts, doxycycline, ethambutol, isoniazid, metronidazole, propranolol, pyrazinamide, and quinidine are all very high. Thus, even though the highest single dose recommended in the SmPC is higher than the highest dosage strength available, the D/S ratio is still beneath 250 mL. Therefore, neither the BCS classification nor the biowaiver recommendation is changed for these APIs.[7,15–22]

The D/S ratio of diclofenac, mefloquine, and rifampicin already exceeded the 250 mL using the 2001 EMEA definition of dose, consistent with their classification according to the US FDA and WHO criteria. Therefore, the increase in the dose associated with the new definition leads to the D/S ratio exceeding the criterion by an even wider margin: the BCS classification of these API is thus not affected.[23–26] Although amitriptyline did not meet the criterion for highly soluble at pH 7.5 (US FDA criterion) at the highest dose strength, it had been decided to make a positive biowaiver recommendation based on the high solubility at pH values up to 6.8 and the risk analysis. In the EU and Martindale, current recommendations for dosing are up to 150 mg/day in divided doses for ambulatory patients and 300 mg for patients being treated in hospital. Under the current EMA guideline, even the highest ambulatory daily dose falls within the D/S criterion over the pH range 1–6.8. Thus, for amitriptyline HCl, no change in the biowaiver recommendation is necessary.[27]

For the 22 APIs considered above, the new definition of D/S by the EMA has thus no impact on the BCS classification or biowaiver recommendation for the API at all. The five remaining APIs require some additional discussion.

For acetazolamide, the BCS classification is affected, as indicated in Table 1, but the biowaiver decision is not. The highest administered dose of acetazolamide is twice the highest dose strength. This leads to a shift in the classification of acetazolamide to from highly soluble to not highly soluble, that is, Class I/III to Class II/IV. Because of the uncertainty about the permeability and dissolution data, the authors of the biowaiver monograph came to the conclusion that acetazolamide was not a good candidate for the biowaiver procedure.[28] Application of the EMA 2010 criterion for D/S would underscore this decision.

At the highest dosage strength for metoclopramide hydrochloride, 10 mg, the D/S is 236 mL. The maximum single dose recommended in the SmPC, 20 mg, leads to a "new" D/S of 472 mL, considerably higher than the cut-off value of 250 mL. According to the EMA guideline, metoclopramide would be reclassified as a class IV drug and therefore would not be eligible for a biowaiver in European jurisdictions.[29]

Similarly, although the highest dosage strength for verapamil hydrochloride, 120 mg, leads to a D/S ≈250 mL, the highest recommended single dose is 240 mg, leading to a D/S ≈500 mL. Thus, verapamil, like metoclopramide, would no longer be eligible for a biowaiver according to the EMA guideline.[7]

For prednisolone, the daily dose can vary over a large range: according to Martindale, usual oral doses range from 2.5 to 60 mg daily in divided doses, as a single daily dose after breakfast, or as a double dose on alternate days. The maximum dosage strength commercially available in Europe was 50 mg according to the biowaiver monograph. At 100 mg, which would be an unusually high dose, the D/S ratio exceeds the cut-off of 250 mL, formally rendering it ineligible for a biowaiver, even though it is "highly soluble" over the usual, lower dose range. The situation is similar for prednisone, noting that it is less soluble than prednisolone and thus at the same dose, will have a less favorable D/S ratio. Strictly adhering to the D/S ratio and considering a maximum single dose of about 100 mg, the 250-mL threshold is exceeded and prednisone would formally fail to qualify for a BCS-based biowaiver.

In the biowaiver monographs,[25,30] it had been argued that the higher doses may not be the most clinically relevant ones to apply to the D/S ratio calculation, noting that when these APIs are given at the higher doses, these are often split up over the day rather than being given as a single dose. Basing the calculation on the more commonly applied lower doses would keep the option of biowaiving open for prednisolone and perhaps also for prednisone.

So the BCS classification of four of the 27 APIs considered was changed when the current EMA definition of dose was applied. The biowaiver recommendations for two of these are no longer valid according to EMA criteria, whereas one remains negative. For the fourth one, prednisolone, a reevaluation of the biowaiver recommendation seems appropriate, which may be considered for related API prednisone as well. More recent biowaiver monographs that already took account of the current EMA guideline, identified quinine sulfate as an additional API for which BCS classification may depend on the regional requirements.[31] These examples illustrate the relevance

Table 1. Overview of APIs Reevaluated Based on Updated EMA Definition of Dose

	API	Highest Dose Strength (mg)	Former Highest Corresponding *D/S* Ratio (mL)	Maximum Single Dose (mg)	Corresponding Indication	New highest Corresponding *D/S* Ratio (mL)	Change in BCS Classification?	Change in Biowaiver Decision?
1.	Acetaminophen[a,b]	500	21	1000	Severe pain	42	No	No
2.	Acetazolamide[a,c]	250	203	500	Starting dose for the treatment of secondary glaucoma or prior to a surgical intervention	406	Yes	No
3.	Acyclovir[a,d]	800	348	800	Treatment of herpes zoster infection	348	No	No
4.	Amitriptyline HCl[a,e]	150	832	300	Treatment of severe depressions	1664	No	No
5.	Atenolol[a,f]	100	4	100	Treatment of high blood pressure and angina pectoris	4	No	No
6.	Chloroquine salts[a,g,h]	155 (base)	1.55	600 (base)	P. falciparum and P. malariae infections	6	No	No
7.	Cimetidine[a,i]	800	133	800	Gastric and duodenal ulceration	133	No	No
8.	Ciprofloxacin HCl[a,j]	750	10,608	750	Different types of bacterial infections	10,608	No	No
9.	Diclofenac sodium[a,k]	50	50,000	75	Treatment of pain in rheumatoid arthritis	75,000	No	No
10.	Doxycycline hyclate[a,l]	200	8	300	Primary and secondary syphilis infection	12	No	No
11.	Ethambutol DiHCl[a,m]	500	<1	2500	Mycobacterial infection	5	No	No
12.	Furosemide[a,n]	500	35,714	500	Acute edemas	35,714	No	No
13.	Ibuprofen[a,o]	800	21,053	800	Severe pain	21,053	No	No
14.	Isoniazid[a,p]	300	2	1200	Intermittent treatment of tuberculosis infection	8	No	No
15.	Mefloquine HCl[a,q]	250	908	750	Treatment of acute nonimmunized patients (>60 kg) infected with malaria	2724	No	No
16.	Metoclopramide HCl[a,r]	10	236	20	Relief of symptomatic gastroesophageal reflux	472	Yes	Yes
17.	Prednisolone[a,s]	50	206	100	See *Results and Discussion*	412	Yes	Yes?
18.	Prednisone[a,t]	50	376	100	See *Results and Discussion*	752	No	Yes?
19.	Propranolol HCl[a,u]	80	0.8	160	Hypertension	1.6	No	No
20.	Pyrazinamide[a,v]	400–500	18.6	2000	Treatment of tuberculosis	99	No	No
21.	Quinidine sulfate[a,w]	300	27	400	Several indications, for example, cardiac arrhythmias	36	No	No
22.	Ranitidine HCl[a,x]	300	0.55	300	Reflux oesophagitis and ulcus pepticum	0.55	No	No
23.	Rifampicin[a,y]	600	938	900	Treatment of brucellosis	1407	No	No
24.	Verapamil HCl[a,z]	120	250 (pH 7.3)	240	Arrhythmias and hypertension	500 (pH 7.3)	Yes	Yes

[a] Sweetman SC (ed), 2012. Martindale: The complete drug reference. [online] London, UK: Pharmaceutical Press. http://www.medicinescomplete.com/Accessed January 17, 2013.
[b] Paracetamol 500 mg, tabletten. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h20572.pdf.
[c] Diamox, tabletten 250 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h00643.pdf.
[d] Zovirax 400 mg, dispergeerbare, filmomhulde tabletten. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h17156.pdf.
[e] Tryptizol 50 mg, filmomhulde tabletten. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h05845.pdf; recommended to take highest dose of 300 mg in divided doses.
[f] Atenolol Sandoz 100, tabletten 100 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h14706.pdf.
[g] Avloclor tablets. Astra-Zeneca. Accessed January 17, 2013, at: http://www.medicines.org.uk/emc/medicine/2272/SPC/Avloclor+Tablets/#POSOLOGY.
[h] Nivaquine, tabletten 100 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h00303.pdf (chloroquine sulfate).
[i] Cimetidine 800 mg Teva, tabletten. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h17233.pdf.
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[n] Furosemide 500 mg Teva, tabletten. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h106750.pdf.
[o] Ibuprofen Actavis 800 mg, filmomhulde tabletten. Accessed June 15, 2011, at: http://db.cbg-meb.nl/IB-teksten/h101818.pdf—this product is no longer marketed in The Netherlands.
[p] Isoniazide Apotex 200 mg, tabletten, dose calculated assuming a body mass of 80 kg and a dose of 15 mg/kg. Accessed May 30, 2013, at: http://db.cbg-meb.nl/IB-teksten/h52497.pdf.
[q] Lariam, tabletten 250 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h11154.pdf.
[r] Primperan tabletten, tabletten 10 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h05250.pdf.
[s] Prednisolon Sandoz 20 mg, tabletten. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h106140.pdf.
[t] Prednison 5 PCH, tabletten 5 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h50970.pdf.
[u] Propranolol HCl 80 PCH, tabletten 80 mg. Accessed January 17, 2013, at: http://db.cbg-meb.nl/IB-teksten/h10218.pdf.
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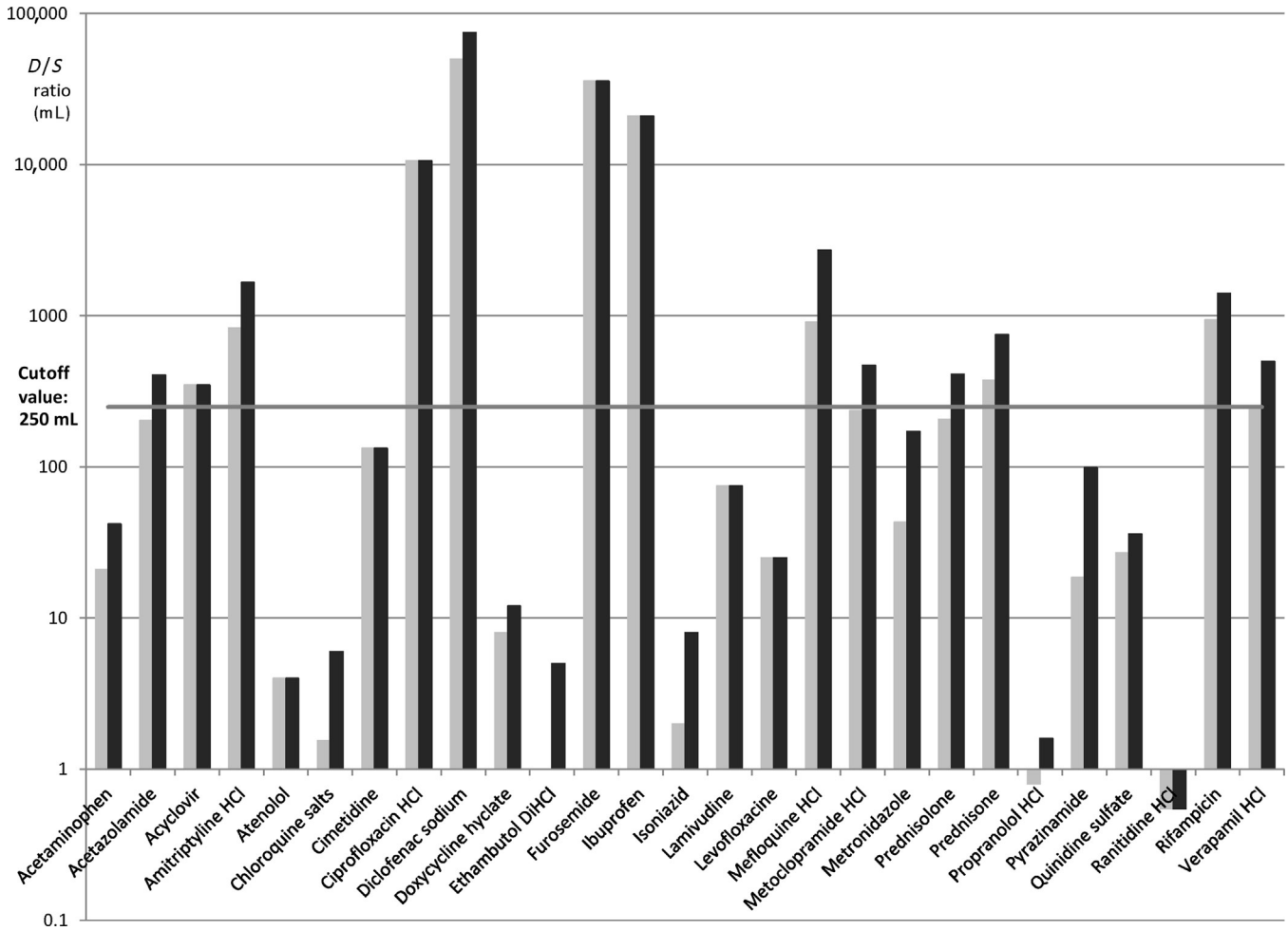

Figure 1. Dose–solubility ratio of APIs according to the previous definition (gray bars) and the new definition (black bars). The horizontal line shows the cut-off value of 250 mL.

of a case-by-case review of biowaivers, especially for substances with borderline solubility characteristics.

It is of note that the new definition of dose in the EMA regulatory guideline for biowaiving is based on the "worst-case" situation that might occur in clinical practice. The examples show that, quite often, the maximum single dose recommended for administration is twice as high (or more) than the highest dose strength available on the market. At the highest administered single dose, there will be the greatest level of challenge for the entire dose to be dissolved in the fluids available. The fluid volume used in the BCS calculation is based on fasted state administration. Depending on the recommendation for conditions of administration, this may also be a "worst-case" situation, because when the drug product is administered with or after a meal, volumes available in the stomach will often be considerably higher than the 250 mL used for the calculation. With the EMA definition, access to biowaiving has thus become more conservative, with the result that APIs with borderline solubilities may be transferred from BCS class I to class II or from class III to IV, rendering them ineligible for the biowaiver procedure.

Interestingly, the new definition of dose is not in line with the dosing requirements for *in vivo* bioequivalence studies, as set out in the very same EMA 2010 guideline. In the section of the guideline addressing *in vivo* studies, it states that these are generally to be carried out with the highest dose strength of API commercially available. The overview of comments on the draft guideline clarifies that this was so decided for feasibility (practical and ethical) reasons, although the highest administered dose was originally preferred from a scientific point of view.[32] Likewise, in the section dealing with biowaivers for lower doses, it is expected that a bioequivalence study has been carried out at the highest dosage strength, not at the highest single dose recommended in the SmPC. Considering that the biowaiver procedure is clearly to be regarded as a surrogate for an *in vivo* bioequivalence study, it appears that the different recommendations for the dose to be used in different sections of the guideline are somewhat inconsistent.

The discussion of the deviation of the EMA dose also raises the question of what is actually the relevant single dose. As illustrated by the case of prednisolone and prednisone, the situation can arise that just a few of the indications or a loading dose could require an exceptionally high dose, whereas for most indications and/or for long term therapy, a much lower dose would be appropriate. To select the appropriate dose for calculation of the D/S ratio, one could take into account the prevalence of the various indications to assess how frequently the API would be administered at an exceptionally high single

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dose level. Another aspect of this risk analysis would be the environment (ambulatory or hospitalized) in which the indication is usually treated. The prevalence of the indication combined with an evaluation of the risk of using a bioinequivalent formulation for that specific indication could be used to define "unusual" and "usual" doses, as illustrated above.

Of course, the regulatory consequences of such a risk evaluation on a generic application would need to be taken into account. The bioequivalence guidelines are in principle aimed at obtaining therapeutic equivalence of reference and test product at all claimed indications, including those for which several doses are administered together. If conclusions are made based on a lower dose, a risk of undetected lack of equivalence for the higher doses will exist. However, the current EMA guideline, as well as the US FDA and WHO guidance documents, already implicitly accept this risk as negligible as they all recommend that the *in vivo* bioequivalence study should in general be conducted at the highest dosage strength, not the highest recommended single dose.

Diverging biowaiver recommendations in the various jurisdictions do not facilitate the application of biowaivers by pharmaceutical industry in daily regulatory practice. For this and the foregoing reasons, it seems that the dose definition used by the US FDA and the WHO is more straightforward to implement and is more consistent with the bioequivalence guidelines in general, whose intent after all is to test the therapeutic equivalence of two given drug products.

CONCLUSIONS

The change in definition of the dose, and hence D/S in the BCS classification calculation by the EMA has an impact on the BCS-based biowaiver recommendation for four of the 27 APIs examined. With the change in definition of dose made by the EMA, the biowaiver recommendations for metoclopramide and verapamil are no longer valid in European jurisdictions. For prednisolone and perhaps also for prednisone, a reevaluation of the biowaiver recommendation, taking into account usual dosing levels, would be appropriate.

The new definition of dose in the EMA regulatory guideline for biowaiving is based on clinical considerations. However, this definition is not yet applied in other bioequivalence guidelines, nor is it in line with the dose definition for *in vivo* bioequivalence studies. It would be helpful if the regulatory authorities would clarify these aspects.

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