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Rapid communication

Scientific considerations concerning the EMA change in the definition of "dose" of the BCS-based biowaiver guideline and implications for bioequivalence

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ABSTRACT

This work discusses the scientific aspects of the definition of dose as the 'highest single oral IR dose' recommended for administration in the SmPC (summary of product characteristics) in the current European Medicines Agency (EMA) 2010 Guideline, for the purpose of biopharmaceutics classification system (BCS)-based biowaiver decision making. Analysis of theoretical and experimental data dealing with drug dissolution and biopharmaceutic drug classification reveals that the drug dose is an important parameter for both drug dissolution and biopharmaceutic classification. The relevant implications for the dose considerations in bioequivalence studies are also discussed briefly. It is suggested that the concept of "the highest single dose oral IR dose recommended for administration in the SmPC" of the EMA 2010 Guideline be abolished. It is advisable, each dose strength be considered separately *i.e.*, whether or not it meets the solubility–dissolution regulatory criteria.

1. Introduction

The introduction of biopharmaceutics classification system (BCS) by Amidon et al. (1995) was followed by a series of guidelines dealing with the waiver and the requirements of the bioequivalence studies (FDA, 2000 EMA, 2001; 2010b). According to BCS, all substances can be classified in four classes (I, II, III, IV), which correspond to the four pairings of "high" or "low" solubility and permeability *i.e.*, the two fundamental drug properties controlling oral drug absorption. Class I compounds are those exhibiting high solubility and high permeability; for a Class I drug, the company can submit an application based on biowaiver justification to the drug agencies if the product is to be marketed as an oral immediate release (IR) formulation.

One of the requirements of both the previous EMA (2001) Guideline and the current FDA (2000) Guideline specifies that "the (marketed) highest dosage strength" should be dissolved in 250 mL for getting the biowaiver status regarding the solubility criterion. However, the recent revised EMA (2010b) Guideline defines dose as the 'highest single oral IR dose' recommended for administration in the SmPC. The impact of this change has been analyzed very recently (Sediq et al., 2014) in terms of the biowaiver monographs published in the literature for 27 active pharmaceutical ingredients (APIs). This analysis (Sediq et al., 2014) follows the principles of the dose/solubility ratio introduced by Rinaki et al. (2003b) and incorporated in the WHO (2006) BCS Guideline; the work of Sediq et al. (2014) relies exclusively on the impact of the change in the nominator of this ratio on the biopharmaceutical classification of 27 APIs.

This work focuses on the scientific aspects of the EMA change in the definition of dose. Since drug guidelines are or should be scientifically based, this rapid communication will focus on the importance of dose in the various *in vitro* and/or *in vivo* drug processes related, among others, to dissolution, biopharmaceutic classification, *in vivo* precipitation and re-dissolution. It will be shown that the EMA change in the definition of dose, although aiming to cover all possible clinical uses of a drug, not only makes more difficult the classification of drugs in Class I but also this change is contrary to the scientific evidence which points in the opposite direction. The implications of the EMA change in the definition of dose for bioequivalence will also be discussed briefly.

2. Maximum single dose defined in SmPC is generally higher than the highest dose strength

Simple visual inspections of the 27 APIs data (Sediq et al., 2014) indicate that the values of maximum single dose defined in SmPC are either the same or in most cases higher than the highest dose

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strength. The SmPC dose defined values can be fourfold (isoniazid, pyrazinamide) or even fivefold (ethambutol diHCl) higher than the highest dose strength (Sediq et al., 2014). Similar analysis of several non steroidal antiinflammatory drugs (NSAIDs) indicates that the increase of the (maximum single dose)/(highest dose strength) ratio can range from 1.0 to 3.3 (Table 1). The maximum single dose administered as an IR oral drug product was obtained from the relevant summary of product characteristics (SmPC) as published on the website of the Medicines and Healthcare Products Regulatory Agency (UK), accessed 12 September 2014 (http://www.mhra.gov.uk). The European innovator product was used and if not available, then the relevant information was obtained from the SmPC of generic products. Similar results for the (maximum single dose)/(highest dose) strength ratio can also be obtained by drug substances from other therapeutic categories.

3. The effect of the dose/solubility ratio on the mean dissolution time (MDT)

The value of MDT is a characteristic of the drug dissolution process since expresses globally the mean dissolution behavior of drug solid particles. According to the common wisdom based on textbooks, MDT is equal to the reciprocal of the dissolution rate constant assuming the diffusion layer model (Noyes–Whitney equation). However, this applies only to a special case, namely, when the dose is equal to the amount needed to saturate the dissolution medium (Rinaki et al., 2003a). In all other cases, MDT is dependent on the dimensionless dose/solubility ratio, q when the drug is completely dissolved (Rinaki et al., 2003a),

$$\mathrm{MDT} = \frac{q - (q-1)\ln(1-q)}{kq} \quad (1)$$

where k is the first-order dissolution rate constant.

For incompletely dissolved drugs the MDT is infinite and the value of mean dissolution time for saturation $(\mathrm{MDT})_s$ is used to express the time for saturation (Rinaki et al., 2003a); obviously, $(\mathrm{MDT})_s$ is heavily dependent on the saturation level which reflects the solubility properties of the API.

Based on the above considerations, which indicate that the dissolution kinetics depend on dose, one can encounter the following scenario: the dissolution requirements (% dissolved at specified time) using the highest dose strength of the current dissolution tests can meet the dissolution criteria while the corresponding solubility requirements based on a high SmPC defined dose could not be fulfilled. The main purpose of dissolution testing is to ensure immediate release properties and prove similarity between the investigative products, while the main purpose of solubility testing is to classify the substance into one of the available classes of the BCS system, or more precisely whether or not the drug belongs to Class I or III. Although the revision of dose definition may have a scientific basis on the fact that it reflects an effort to cover all possible clinical uses of a drug, both solubility and dissolution tests ultimately serve the same regulatory purposes, that is biowaiving decision making and finally serving as surrogate for *in vivo* bioequivalence studies. Therefore, the use of two different doses in the two relevant sets of experiments is unjustifiable. These observations are very appropriate for Class II compounds since relevant concerns have been raised in the past for the failure of NSAIDs to meet the dissolution criteria despite of the fact that these drugs exhibit extensive absorption (Yazdanian et al., 2004). Intuitively, the use of a high SmPC defined dose in solubility experiments for some of NSAIDs will make the solubility requirements insuperable. It is worthy to mention that the extensive absorption of NSAIDs has been explained with a dynamic model of drug dissolution-uptake (Rinaki et al., 2004) followed by the publication of a biowaiver monograph of ibuprofen (Potthast et al., 2005) which belongs to the NSAIDs. Also, it is very well known that apart from drug dissolution, GI phenomena like drug

Table 1
Overview of NSAIDs evaluation of (maximum single dose)/(highest dose strength) ratio.

API	Highest dose strength (mg)	Maximum single dose (mg)	(Maximum Single dose)/(highest dose strength) ratio
Diclofenac[a]	50	75	1.5
Etodolac[b]	300	600	2.0
Indomethacin[c]	50	100	2.0
Sulindac[d]	200	200	1.0
Fenoprofen[e]	300	1000	3.3
Flurbiprofen[f]	100	150	1.5
Ibuprofen[g]	400	400	1.0
Ketoprofen[h]	100	100	1.0
Naproxen[i]	500	1000	2.0
Mefenamic acid[j]	500	500	1.0
Acetyl-salicylic acid[k]	300	300	1.0
Diflunisal[l]	500	1000	2.0
Meloxicam[m]	15	15	1.0
Piroxicam[n]	20	20	1.0
Celecoxib[o]	200	400	2.0

[a] Voltarol 50 mg tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1396241785062.pdf).
[b] Eccoxolac 300 mg hard capsules (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1364967162885.pdf).
[c] Indocid 50 mg capsules (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1407476809193.pdf).
[d] Sulindac 200 mg tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1392966614096.pdf).
[e] Fenopron 300 mg film coated tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1357532316947.pdf).
[f] Flurbiprofen 100 mg film coated tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1405662905639.pdf).
[g] Advil 400 mg tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1409896245584.pdf).
[h] Ketoprofen 100 mg capsules BP (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1408342760679.pdf).
[i] Naprosyn 500 mg tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1366696851258.pdf).
[j] Ponstan forte 500 mg film coated tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1392966485277.pdf).
[k] Aspirin 300 mg gastro-resistant tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1386225579867.pdf).
[l] Diflunisal 500 mg film coated tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1398405440514.pdf).
[m] Meloxicam 15 mg film coated tablets (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1397197140602.pdf).
[n] Feldene 20 mg capsules (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1390535182906.pdf).
[o] Celebrex 200 mg hard capsules (http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1402034401474.pdf).

precipitation or re-dissolution in the lumen are strongly dependent on dose administered (Psachoulias et al., 2012). However, even the most recent drug precipitation studies are of pure physicochemical nature and do not take into account the dose used (Thorat et al., 2014). Consequently, it is scientifically sound to perform dissolution tests based on the dose used in actual practice *i.e.*, specific *in vitro* dissolution requirements for each single dose used in practice, although it is acknowledged that there may be some potential difficulties in experimental conditions resulting from running more than one unit per vessel in a dissolution testing.

4. The unknown role of dose in reaction limited dissolution processes

The constant diffusion layer throughout the dissolution process for diffusion-controlled dissolution has been criticized as unphysical (Wang et al., 2012). Several alternatives based on what we call reaction-limited model of dissolution have been proposed (Dokoumetzidis and Macheras, 1997; Lánský and Weiss, 1999; Dokoumetzidis et al., 2008; Charkoftaki et al., 2011). All these approaches rely on the reaction of drug solid particles (dose) with the solvent species (dissolution medium or GI lumen fluids). Although the characteristics *e.g.*, stoichiometry, surface morphology of the drug particles of this reaction under *in vitro* and *in vivo* conditions are unknown, one can anticipate dramatic changes in the kinetics of the dissolution process if one of the main reactant species (drug particles, dose) will be altered *i.e.*, from the highest dose strength to the SmPC defined dose. Due to the unstirred conditions prevailing in the GI tract, this mechanism might be very important for the *in vivo* dissolution of sparingly soluble drugs. Our ignorance for the exact drug dissolution mechanisms operating under *in vivo* conditions calls for specific *in vitro* dissolution requirements for each single dose used in practice.

5. The use of the dose/solubility ratio for biopharmaceutic classification purposes

It has been found that the dose/solubility ratio is not a static parameter and the dynamic role of the reciprocal of dose/solubility ratio in driving the dissolution rate (Rinaki et al., 2003a) justified its use for biopharmaceutic classification purposes (Rinaki et al., 2003b). Several years later these concepts were utilized for the introduction of developability classification system (Butler and Dressman, 2010). For both systems (Rinaki et al., 2003b; Butler and Dressman, 2010) the dose is a crucial parameter for biopharmaceutic classification and this has been recognized in the WHO (2006) Guideline. These findings inextricably link the dose as well as the solubility and dissolution requirements with biopharmaceutic classification and point to the fact that different doses should not be used in the *in vitro* solubilityand *in vitro* dissolution tests. Moreover, each one of the dose strengths should be considered independently since the driving force of the dissolution rate is the specific value of the reciprocal of dose/solubility ratio for each one of the actual doses used in practice.

6. Drug class migration as a function of dose

Analysis of bioavailability data of drugs used in various dose strengths resulted in a dose dependent version of BCS (Charkoftaki et al., 2012). According to this scheme a drug used in low doses can behave as a Class I drug while the same drug used in higher doses above a critical dose level can be classified in Class II. Obviously, this dose dependent class migration is strongly associated with the replacement of the highest dose strength with the SmPC defined dose. In the same vein, the recently developed ABΓ system, a non-binary version of BCS, is based on the continuity of absorption and includes a dose dependency in the biopharmaceutic classification of drugs (Macheras and Karalis, 2014).

The analysis presented above indicates that the dose is not a "static" parameter. Its use should not be limited to the "initial conditions" required for the solution of differential equations expressed in terms of the amount of drug in the system (Amidon et al., 1995). Similarly, the everyday expressions "per cent dissolved", " per cent absorbed", 'per cent metabolized" should be replaced by "per cent of dose dissolved", "per cent of dose absorbed", 'per cent of dose metabolized", respectively. This simple change is necessary in order to emphasize that the specific value associated with each one of the processes is dependent on the dose used in the experiment or study. Ideally, this change should be adopted by the official compendia. Finally, a word of caution is required for the dramatic effect of dose on carrier mediated transport in the GI tract or the hepatic elimination following Michaelis–Menten kinetics. These aspects are beyond the scope of this work.

7. Implications for bioequivalence

To the best of our knowledge, the dose related bioequivalence requirements did not change in the EMA (2010b) Guideline. In fact, the dose related bioequivalence requirements have to follow the principles of the corresponding dose related solubilityand dissolution criteria. Currently, there is an ambiguity for the potential use in bioequivalence considerations of the 'highest single oral IR dose' recommended for administration in the SmPC and applied to the solubilitycriteria. Although the highest single oral dose was originally preferred during the drafting of the guideline from a scientific point of view (EMA, 2008), it was acknowledged that there are a number of difficulties, both practical and ethical, with such recommendation (EMA, 2010a). Therefore, the guideline has finally been revised, in general, to recommend the use of the highest tolerable strength in healthy volunteers.

However, the former analysis provides scientifically based arguments for the use of specific solubility-dissolution criteria for each one of the actual doses used in practice. This observation can be extended to the *in vivo* effective solubility and the critical dose concepts developed by Charkoftaki et al. (2012) for bioequivalence purposes. Hence, an upper dose limit (critical dose) for bioequivalence studies may be fixed whenever the *in vivo* data demonstrate a linear AUC-dose relationship (Charkoftaki et al., 2012). This type of results can guide dose selection criteria for bioequivalence studies in future revisions of the EMA Guideline.

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