Journal of Pharmaceutical Sciences Volume 95, Issue 5, Pages 974-984

Published Online: 23 Mar 2006

Biowaiver monographs for immediate release solid oral dosage forms: Cimetidine

E. Jantratid 1 2, S. Prakongpan 1, J.B. Dressman 2, G.L. Amidon 3, H.E. Junginger 4, K.K. Midha 5, D.M. Barends 6 *

1 Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand
2 Institut für Pharmazeutische Technologie, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany
3 College of Pharmacy, University of Michigan, Ann Arbor, Michigan
4 Leiden/Amsterdam Center for Drug Research, Leiden University, Division of Pharmaceutical Technology, Leiden, The Netherlands
5 University of Saskatchewan, Saskatoon, Saskatchewan, Canada
6 RIVM, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

email: D.M. Barends (Dirk.Barends@RIVM.nl)

*Correspondence to D.M. Barends, RIMV, National Institute for Public Health and the Environment, Bilthoven, The Netherlands. Telephone: +31 30 2744209; Fax: +31 30 2744462

This paper reflects the scientific opinion of the authors and not the policies of regulating agencies.

Abstract

Literature data relevant to the decision to allow a waiver of in vivo bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing cimetidine are reviewed. According to the current Biopharmaceutics Classification System (BCS), cimetidine would be assigned to Class III. Cimetidine's therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions, and reported BE/bioavailability (BA) problems were also taken into consideration. On the basis of the overall evidence, a biowaiver can be recommended for cimetidine IR products, provided that the test product contains only those excipients reported in this paper in their usual amounts, and that the test and the comparator drug products both are rapidly dissolving as per BCS. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 95:974-984, 2006

INTRODUCTION

A monograph is presented on cimetidine with respect to the possibility of waiving in vivo bioequivalence (BE) testing for the approval of new and/or reformulated immediate release (IR) solid oral dosage forms. The purpose and scope of this series of monographs were discussed previously.[1] Briefly, the aim of these monographs is to evaluate all pertinent data available from literature sources, for Active Pharmaceutical Ingredients (APIs) listed on the WHO List of Essential Medicines[2] and/or in common use, with a view to assess whether a biowaiver is appropriate or not, and if appropriate, under which restrictions. In this risk assessment, risk is defined as both the likelihood of an incorrect application of the biowaiver and the consequences of such an incorrect biowaiver decision in terms

of public health and patient's risk. Monographs have previously been published for verapamil, propranolol, atenolol, chloroquine, ranitidine hydrochloride, ibuprofen, acetaminophen, and amitryptiline.[1],[3-7] Although in April 2003, cimetidine was replaced by ranitidine on the WHO List of Essential Medicines, its continued widespread use justifies the inclusion of cimetidine in this series.

GENERAL CHARACTERISTICS

Name

INN name: Cimetidine, Chemical name: N-cyano-N-methyl-N-[2([(5-methyl-1H-imidazol-4-yl)methyl]thio)ethyl] guanidine. Its structure is shown in Figure 1.

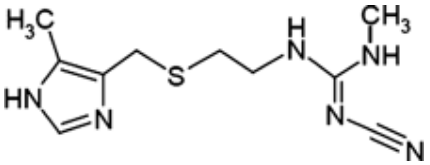

Figure 1. Structure of cimetidine.

Therapeutic Indication

Cimetidine is one of several histamine H2-receptor antagonists widely used in conditions where inhibition of gastric acid secretion may be beneficial, such as duodenal and gastric ulcers.[8-11] It reduces pepsin output and competitively inhibits the action of histamine at the histamine H2-receptors of the parietal cells.[9-11]

Therapeutic Index and Toxicity

In general use, the total daily dose by any route of administration should not exceed 2.4 g, whereas the standard dosage is 800 mg.[9] However, no clinically significant adverse drug reactions were found in a study evaluating the toxicity of a cimetidine overdosage of 5.2-20 g in patients with normal kidney function, including one patient who received cimetidine 12 g/day for 5 days.[8],[9] Adverse drug reactions to cimetidine are infrequent, occurring with an incidence of about 5%.[11] These effects are usually reversible following a reduction of dosage or withdrawal of therapy.[8],[9],[11] Accordingly, it can be concluded that cimetidine has a wide therapeutic index.

CHEMICAL PROPERTIES

Salt, Esters, Polymorphs

A hydrochloride salt of cimetidine exists,[9],[12],[13] but is used only in liquids and injections. This monograph pertains to the free base only.

Four polymorphs of cimetidine, forms A, B, C (anhydrous), and D (monohydrate) have been reported.[14-17] The polymorphic form was shown to affect the physicochemical properties, the BA, as well as the clinical efficacy of cimetidine.[14],[15] The dissolution rate constant in water for form C was found to be 1.29, 1.70, and 1.90 times greater than those measured for forms A, D, and B, respectively.[14] However, polymorphic form A was found to be the easiest to tablet as well as physically stable and it is therefore used in all commercially available cimetidine drug products.[14],[17]

Solubility

Cimetidine is slightly soluble in water.[9] Its aqueous solubility is 11.4 mg/mL at 37°C at a final pH of 9.3.[8],[10] The minimum solubility determined in the pH range 1-8 at 37°C is 6 mg/mL.[18]

Partition Coefficient

The n-octanol/water partition coefficient (log P) of cimetidine was reported as 2.5 at pH 9.2.[8] Calculations using fragmentation methods based on atomic contributions to lipophilicity and by using the C log P program (version 3.0, Biobyte Corp, Claremont, CA, http://www.biobyte.com) gave values of 0.35 (C log P) and 0.79 (log P).[19] Other workers reported a log P value of 0.48,[20] being most probably log D values obtained at lower pH values.

pKa

Cimetidine is weakly basic with the pKa values reported as 6.80[8] and 6.93.[20] It is thus present, at least partly, in the ionized form in the upper gastrointestinal (GI) tract.

Dosage form Strengths

Strengths with a Marketing Authorization (MA) in Germany (DE) and the Netherlands (NL) contain 200, 400, and 800 mg. In Finland (FI), only the 400 mg strength has a MA.

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Cimetidine is rapidly, yet incompletely absorbed after oral administration. Its BA is between 56%-68% in healthy subjects and about 70% in patients with peptic ulcer disease, in whom a much greater variation in absorption was observed.[8],[11],[21] In the fed state, the absorption of cimetidine is slightly delayed but the extent absorbed is not significantly different to that in the fasted state.[22] A BA study in a patient with a massive bowel restriction demonstrated reduced absorption of cimetidine, which was attributed to rapid transit of the drug through the GI tract.[23] Both the absorption and clearance of cimetidine are linear in the therapeutic dosing range.[8],[21],[22],[24] Using the everted ring technique, the uptake of cimetidine from the rat jejunum and colon was shown to be linear in the range of 0.0005-40 mM.[25] After oral administration in the fasted state, cimetidine usually shows erratic double peak or multiple peak phenomenon in plasma drug concentration-time profile.[8],[21],[22],[26] The phenomenon has been described extensively and still under discussion.[27-33] However, secondary peaks occur independent of the formulation.[26] As such, the double peak phenomenon is not relevant for the consideration of a biowaiver.

Permeability

The permeability values of cimetidine obtained from various studies are shown in Table 1. Based on a single-pass intestinal perfusion study of cimetidine across jejunal epithelia and intestinal uptake in rats, it was suggested that paracellular pathway plays an important role to cimetidine transport.[25],[34] The mechanisms of cimetidine permeability leading to low absorption have been reported.[34-37] Intracellular cimetidine and its major metabolite, the S-oxide, were shown to be regulators of absorption of cimetidine via the paracellular route.[34],[37] In addition, using Caco-2 monolayers as an in vitro model for studying transport of cimetidine and the other H2-antagonists, it was found that this group of APIs have the potential to reduce their own epithelial permeability via tight junction modulation.[35] Further, they are substrates for intestinal P-glycoprotein in efflux mechanism.[36]

Table 1. Permeability of Cimetidine

Method	P_{app}/P_{eff} ($\pm 10^{-6}$) (cm/s)	Reference
	35	[53]
Human jejunal perfusion[a]	29.6 ± 13.9	[54]
	30.4 ± 19.8	
Caco-2[c]	0.50	[55][b]
HT29-18-C_1[d]	4.0	
Human jejunum	77	
Human ileum	26	
Caco-2[e]	3.06	[57]
Caco-2[f,g]	0.65 ± 0.007 (AP → BL)[h]	[41]
	2.18 ± 0.12 (BL → AP)[h]	
Caco-2[i]	0.74 ± 0.09 (pH 7.2)	[58]
	0.50 ± 0.02 (pH 5.4)	
Caco-2	0.65 (AP → BL)[h]	[59]
	2.18 (BL → AP)[h]	
Caco-2[e]	1.37 ± 0.34	[60]
Caco-2	0.75	[61]
MDCK	0.28	
LLC-PK1	1.1	
Caco-2[j]	0.39 ± 0.02	[62]
HT29-MTX[k]	0.86 ± 0.10	
Rat *in situ* single-pass intestinal perfusion[g]		[37]
Rat jejunum pH 5.5	7.8 ± 4.2	
Rat jejunum pH 6.5	14.2 ± 1.9	
Rat jejunum pH 7.5	3.5 ± 1.3	
Rat ileum pH 6.5	7.9 ± 2.1	
Rat ileum pH 7.5	12.8 ± 1.7	

a The data are shown as mean ± SD.
b The authors calculated in vivo Papp based on the data from Reference.[62]
c Transepithelial electrical resistance (TEER) = 300 · cm2.
d TEER = 100 · cm2.
e The integrity of the monolayers was assessed by determining the flux of radio-labeled mannitol for each insert which has to be lower than 0.5%/h.
f [14C] mannitol permeability value less than 1 ± 10-6 cm/s was used as a marker whether the monolayers integrity was acceptable.
g The data is shown as mean ± SEM.
h AP, apical; BL, basolateral.
i [14C] mannitol permeability and TEER values were employed as monolayer integrity markers.
j TEER = 360 · cm2.
k TEER = 980 · cm2.

Distribution

The volume of distribution of cimetidine, whether expressed as at steady-state (Vdss) or the area volume of distribution (Vd), is approximately 0.8-1.39 L/kg.[8],[11],[24] This value decreases with increasing age.[8] The plasma protein binding of cimetidine is as low as 19%[11] and consequently has no clinical and pharmacokinetic significance.

Metabolism and Excretion

Cimetidine and its metabolites are eliminated predominantly via the kidney.[8],[21] About 50%-80% of the dose given intravenously is recovered unchanged in urine.[8] Roughly 50% is obtained after oral administration.[21]

The elimination half-life of cimetidine (t1/2) after intravenous administration is approximately 2 h in healthy adults.[8],[26] Metabolism of cimetidine is accountable for 25%-40% of the total elimination of cimetidine and is dependent on age.[8] With respect to metabolism in the GI tract, the human jejunal perfusion study conducted by Hui et al.[38] demonstrated that cimetidine metabolite constituted 3% and 6% of the initial cimetidine concentration over 50 cm of jejunum in two subjects. The relatively low intestinal permeability and the metabolic processes together seem to be responsible for the low oral BA of cimetidine.

DOSAGE FORM PERFORMANCE

Excipients

A study of the effect of mannitol on cimetidine absorption obtained following administration of chewable tablets or oral solutions containing 200 mg cimetidine formulated with either 2.264 g of radio-labeled mannitol or radio-labeled sucrose demonstrated that the BA after administration of mannitol-containing cimetidine formulations was significantly lower, compared with those which contained sucrose.[39] It was suggested that a reduction of the GI transit time is the major reason for this reduced drug absorption. The amount of mannitol used was higher than the amounts usually present in IR solid oral dosage forms. An indication of the amounts usually present in dosage forms for drug products with a MA in the USA can be obtained from the FDA Inactive Ingredients Database.[40] For mannitol, the highest amount present in IR oral tablets with a MA in the USA is 607 mg,[40] which is less than 1/3 of the amount used in the study cited. The influence of sodium lauryl sulphate on cimetidine absorption has also been studied.[26] The ability of sodium lauryl sulphate to enhance permeability across cell monolayers has been demonstrated.[41] Sodium lauryl sulphate is employed in some formulations, including the innovator, Tagamet®. However, human in vivo results obtained from Tagamet® did not show significant differences when compared with formulations containing no sodium lauryl sulphate.[26]

Several investigations evaluating the effects of excipients have been conducted on the absorption of ranitidine, an API closely related to cimetidine.[42-44] These are discussed in the biowaiver monograph on ranitidine, for which it was concluded that osmotically active excipients in high concentrations reduce ranitdine BA by reducing the GI transit time.[4] This conclusion will be applicable to cimetidine also, in view of the similarity of both APIs and is further supported by the observations with mannitol.

The excipients in cimetidine IR products in DE, FI, and NL are listed in Table 2. In previous monographs MAs of IR solid oral dosage forms were taken as indicators that these drug products had successfully passed an in vivo BE test.[1] However, for cimetidine, this cannot be assumed. The bioavailability committee of the regulatory authorities of DE classified cimetidine in 1998 as an API for which in vivo BE testing was not considered necessary.[45] After the adoption of the European Note for Guidance BA/BE introducing BCS,[46] the authorities in DE harmonized their regulatory system with the European regulations. Thus, removal of cimetidine from the list of APIs for which in vivo BE studies were deemed unnecessary was not based on any incident with specific products and MAs granted under that provision were not revoked.[47] It cannot be excluded that FI and NL also have granted MAs without requiring in vivo BE studies. However, the drug products reported in Table 2 are in therapeutic use, and hence we can assume that, even in the unlikely situation that some of these drug products would not be bioequivalent to the innovator, these drug products are safe and effective.

Table 2. Excipients[a] Present in Cimetidine IR Solid Oral Drug Products[b] with a Marketing Authorization (MA) in Germany (DE), Finland (FI) and The Netherlands (NL), and the Minimal and Maximal Amount of these Excipients Present per Dosage Unit in Solid Oral Drug Products with an MA in the USA

Excipient	Drug Products Containing that Excipient with a MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with a MA in the USA (mg)
Ammonio methacrylate copolymer type B	DE (1)	
Carnauba wax	FI (2)	0.16-58*
Cellulose	DE (1, 3-15); FI (2); NL (16-28)	4.6-1385*
Croscarmellose sodium	DE (1); NL (29-31)	2-180
Crospovidone	NL (25)	4.4-792*
Disodium edetate	DE (15); NL (16, 25)	0.21-4
Gelatin	DE (3, 6, 14)	1-756*
Glycerol	DE (3-6, 14); NL (20)	0.14-198**
Hydroxypropylcellulose	FI (2)	1-132
Hypromellose	DE (1, 3-6, 8, 10-15); FI (2); NL (16-35)	0.8-80
Lactose	NL (27, 29-31, 34, 35)	35-1020*
Macrogol	DE (1, 3-6, 8, 10-14); FI (2); NL (17-22, 24, 27-35)	0.12-500*
Magnesium stearate	DE (1, 3-15); FI (2); NL (16-35)	0.9-401*
Maize starch	DE (3-7, 9, 11, 14, 15); FI (2); NL (16, 20-24, 29-31, 34, 35)	9.9-1135*
Methylcellulose	DE (1)	2.8-184
Polysorbate 80	DE (8,10,12,13)	2.2-418*
Potato starch	NL (27)	2.1-80
Povidone	DE (1, 4, 5, 7-13, 15); FI (2); NL (16-35)	0.17-75
Propylene glycol	DE (15); NL (16, 23, 25, 26)	1.5-52
Silica	DE (1, 3, 6, 8, 10-14); NL (17-19, 28, 35)	0.65-99
Simeticone	DE (1)	0.0004-5.7
Sodium lauryl sulphate	DE (4, 5, 7, 9, 15); NL (16, 19, 20, 22, 25, 29-31)	0.65-50
Sodium starch glycolate	DE (3-15); FI (2); NL (16-28, 32-35)	2-876*
Sorbic acid	DE (1)	0.94
Starch	NL (25)	22-616
Stearic acid	NL (27)	0.9-72*
Talc	DE (1, 8, 10-13); NL (21, 27, 29-32)	0.1-220*
Triethyl citrate	DE (1)	3.6-8.9

Sources of data: DE: www.rote-liste.de (assessed 27/05/2005); FI: www.nam.fi (assessed 13/06/2005); NL: www.cbg-meb.nl (assessed 13/06/2005). USA: http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose (version date 06/05/2005).

1. Cimetidin AL 400/-800 Filmtabletten.
2. Cimex 400 mg tabletti, kalvopäällysteinen.
3. Cime 400/-800 mg AbZ Filmtabletten.
4. Cimebeta® 200/-400/-800 Filmtabletten.
5. CimeHEXAL® 200/-400/-800 Filmtabletten.
6. Cimetidin 200/-400/-800 von ct Filmtabletten.
7. Cimetidin acis® 200/-400/-800 mg Tabletten.
8. Cimetidin AL 200 Filmtabletten.
9. Cimetidin STADA® 200/-400/-800 mg Tabletten.

10. CimLich 200/-400/-800 mg Filmtabletten.
11. DuraH2 400 Filmtabletten.
12. DuraH2 800 Filmtabletten.
13. Gastroprotect® 400/-800 Filmtabletten.
14. H 2 Blocker-ratiopharm® 200/-400/-800 Filmtabletten.
15. Tagamet® 200/-400 mg Filmtabletten.
16. Tagamet 400/800 Tiltab, tabletten 400/800 mg.
17. Cimetidine 200/400/800 PCH, omhulde tabletten.
18. Cimetidine Sandoz 200/400/800, tabletten, MA 15655/6/7.
19. Cimetidine-DP 200/400/800, tabletten.
20. Cimetidine 200/400/800, tabletten Hexal.
21. Cimetidine Gf 200/400 mg, tabletten MA17231/2.
22. Cimetidine 200 mg/400 mg, tabletten Katwijk Farma.
23. Cimetidine 800 mg, tabletten Katwijk Farma.
24. Cimetidine Alpharma 200 mg/400 mg, tabletten.
25. Tagamet-OTC 200, tabletten 200 mg.
26. Cimetidine CF 200/400/800 mg, tabletten.
27. Cimetidine 200/400/800 mg, tabletten Wise Pharmaceuticals.
28. Cimetidine Gf 200/400/800 mg, tabletten MA 56372/3/4.
29. Cimetidine 200/400/800 mg, tabletten GenRx.
30. Cimetidine Sandoz 200/400/800, tabletten MA 23572/3/4.
31. Cimetidine FLX 200/400/800 mg, tabletten.
32. Cimetidine Gf 800 mg, tabletten MA 17233.
33. Cimetidine Alpharma 800 mg, tabletten.
34. Cimetidine 200/400 mg, tabletten Delphi Pharmaceuticals.
35. Cimetidine 800 mg, tabletten Delphi Pharmaceuticals.

a Colorants are not included.

b Dosage forms that are swallowed by the patient in liquid form, such as effervescent tablets, dispersible tablets, and also chewable tablets and oral suspensions, are excluded.

* The upper range value reported is unusual high for solid oral dosage forms and the authors doubt its accuracy.

** The authors doubt the accuracy of these data. Such amounts are normally present in a soft gelatin capsules, but not in capsules, as indicated by FDA Inactive Ingredients Database.

Dissolution

In the cimetidine tablets monograph of the USP,[13] the dissolution specification is not less than 80% (Q) dissolves within 15 min in 900 mL of 0.01 N HCl, using the basket at 100 rpm. For one brand of generic cimetidine tablets, it was demonstrated that both the f2 criterion for the similarity of dissolution profiles[46],[48] and in vivo BE to the innovator were met.[49] The present biowaiver criteria[46],[48] state that, in addition to similarity of dissolution profiles, the test and the comparator drug product should both be rapidly dissolving, which is defined as: not less than 85% of API releases within 30 min, employing the dissolution conditions described therein. This same dissolution method was recently employed for evaluating randomly selected IR cimetidine drug products having a MA in DE and in Thailand.[26] It was found that all these drug products exhibited rapidly dissolving characteristics within the BCS limit. In addition, cimetidine tablets formulated to have distinct release characteristics were investigated to determine the relationship between in vitro dissolution behavior and in vivo absorption. It was found that the dissolution would become rate-determining only when it falls below 85% in 120 min.[26] These results strongly support the permeability rate-limiting properties of cimetidine drug products. Reports of other BCS Class III APIs support these findings.[50-52] Polli et al.[50] demonstrated comparable plasma concentration-time profiles for

ranitidine hydrochloride drug products, which had rapid in vitro release patterns in 900 mL water using paddle method at 50 rpm. The results demonstrated that there were differences in dissolution rate, but all four formulations were found to be bioequivalent in a four-way, single-dose in vivo BE study. The authors concluded that differences in dissolution rates observed earlier than 30 min had negligible consequences in vivo. Similar results were obtained for metformin drug products, noting that metformin is also BCS Class III.[51] Taken together, the data available to date for Class III compounds suggest that, at least for some, the biowaiver procedure may well be appropriate.

DISCUSSION

Solubility

According to the BCS criteria,[46],[48] the D:S ratio of highly soluble drug has to be less than or equal to 250 mL in the physiologically relevant pH range. Therefore, cimetidine is categorized as highly soluble, since its D:S ratio is 133 mL, based on 800 mg being the highest dose strength available and a solubility of 6 mg/mL.[53] This is in line with a Do of 0.53 reported earlier[18] as Do ± 250 = D:S. With a pKa of about 6.8, cimetidine would be even more soluble in more acidic pH conditions, indicating that no solubility-limiting problem is expected for cimetidine in the upper GI tract.

Permeability

The poor permeability characteristics of cimetidine, demonstrated by many studies, are summarized in Table 1. Several APIs, including cimetidine, were evaluated by human perfusion studies for their permeability through the jejunum by Amidon et al.[53] and Takamatsu et al.[54] In these studies, cimetidine was categorized as low permeability relative to the internal high permeability standards propranolol and phenylalanine and the internal zero permeability markers PEG 400 and PEG 4000. These internal standards are also suggested for use in establishing suitability of a permeability method in the FDA guidance.[48] In addition, Collett et al.[55] reported a higher value of cimetidine jejunal permeability compared to those of the aforementioned studies, yet, below the low permeability cut-off of 2 ± 10-4 cm/s.[18] The corresponding fraction absorbed is 0.5[56] and 0.62,[57] in reasonable accordance with the BA values reported.[8],[21],[26] This classification is supported by calculations of permeability based on its partition coefficient; C log P and log P values were lower than for metoprolol, the reference compound.[19]

The cimetidine permeability results obtained from cell cultures are variable and appear to be lower than the values obtained by human perfusion technique (Tab. 1).[58-63] In the previous monographs,[1] similar data have been reported with atenolol, which is also BCS Class III. The differences between in vitro permeability studies via cell cultures and in vivo intestinal perfusion technique in human can be explained. Cimetidine and atenolol are both hydrophilic and are transported paracellularly through the intestinal membrane. This route of transport is less available in cell monolayers, as reflected by the higher transepithelial electrical resistance (TEER) compared with that of cell tissue of the small intestine, and may be responsible for lower permeability of APIs. In addition, types of cell culture, culturing media and transport media used as well as cell line itself are proven sources of variability in permeability evaluation by cell cultures.[64] Accordingly, permeability data obtained by human perfusion appear to be more reliable than those obtained from cell culture systems, especially for APIs transported by paracellular route. Permeability results of cimetidine using in situ single-pass intestinal perfusion in rat are also presented in Table 1.[37] The permeability values obtained in the single-pass intestine perfusion in rat were also lower than those observed in human studies.

In view of all the information evaluated, cimetidine can be reliably classified as not highly permeable.

Surrogate Techniques for In Vivo Bioequivalence Testing
Although only polymorphic form A is used in commercial tablets, it is noted that in vitro dissolution in water was able to detect other polymorphic forms. And if there is sufficient evidence that the excipients in the test product have no effect on the permeability or GI transit time, comparative dissolution testing can provide reasonable assurance for bioequivalency of the test product to its comparator.

In fact, it appears that the f2 criterion for similarity of dissolution profiles represents a rather conservative approach, both for cimetidine and, as previously shown, for other Class III APIs, since the rate-limiting step in the absorption process is the permeability, rather than the dissolution for these APIs.[4] Thus, it appears that the f2 criterion is more than sufficient to assure BE of cimetidine products in the absence of any excipient effects.

Risks for Bioinequivalence Caused by Excipients and/or Manufacturing Parameters
Because permeability is the critical step in the absorption of the BCS Class III APIs, excipients that alter the GI motility and/or membrane permeation have the highest potential to affect the absorption. However, the formulations of IR solid oral dosage forms containing cimetidine seem to exhibit little risk in terms of BE, as can be concluded from the lack of a detectable in vivo interaction with sodium lauryl sulphate.[26] Moreover, the recent study on cimetidine drug products with a current MA in DE and Thailand also showed that there is little risk of reaching an incorrect biowaiver decision when dissolution results are similar.[26]

For the excipients listed in Table 2, it was concluded that there is little risk of clinical issues resulting from substitution for drug products in which these excipients are utilized. This observation is further supported by Yu et al.,[65] which reported that commonly used excipients used to formulate BCS Class III APIs in IR solid oral dosage forms had no significant effect on their absorption. The risk of adverse clinical effects resulting from substitution is likely to be even smaller if an excipient is present in a large number of registered drug products, provided these excipients are present in amounts typically used in IR solid oral dosage forms. When these two criteria are met, together with the rapidly dissolving criterion as per BCS,[46],[48] a high level of assurance for excluding bioinequivalent drug products exists. Hence, for cimetidine, the risks for bioinequivalence caused by excipients and/or manufacturing parameters is smaller than those for IR drug products in general, for which the FDA SUPAC IR Guideline requires in vivo BE qualification of major changes, that is, Level 3 changes in terms of composition and/or manufacturing process.[66] However, as the SUPAC IR Guideline covers also APIs of BCS Class II and IV, it is of necessity more conservative.

Patient's Risks Associated with Bioinequivalence
Cimetidine has a wide therapeutic index and is not indicated for very serious diseases. Therefore, even in the unlikely situation that a bioinequivalent drug product would pass all the qualification criteria summarized above, and hence give rise to supra- or subtherapeutic serum levels, this would be unlikely to result in serious public health concerns.

CONCLUSION

According to the present regulations, cimetidine falls into BCS Class III.[46],[48] Other workers also classified cimetidine as BCS Class III.[19],[67] For IR solid oral drug products, biowaivers currently can only be requested for drug products containing BCS Class I APIs.[46],[48] However, the data evaluated and discussed in this monograph show that it would be safe to grant biowaivers for IR solid oral dosage forms of cimetidine, provided that the test product is formulated with excipients shown in Table 2, in amounts typically used in IR solid oral dosage forms. An indication of the amounts usually present in dosage forms for API products with an MA in the USA can be obtained from the FDA Inactive Ingredients Database.[40] Moreover, both the test product and the comparator drug product must be rapidly dissolving according to the current BCS criteria and the f2 criterion met,[46],[48] although it is noted that the f2 criterion for similarity of dissolution profiles tends to be on the conservative side for cimetidine IR products. Biowaivers for other BCS Class III APIs have also been evaluated to be reasonably safe, provided similar conditions are met.[1],[4],[50-52]

Acknowledgements

Gert Ensing, RIVM is acknowledged for aggregating the data of Table 2. This work was supported in part by the Thailand Research Fund through the Royal Golden Jubilee Ph.D. program (Grant No. PHD/0005/2543).

References

1 Vogelpoel H, Welink J, Amidon GL, Junginger HE, Midha KK, Möller H, Olling M, Shah VP, Barends DM. 2004. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: Verapamil hydrochloride, propranolol hydrochloride, and atenolol. J Pharm Sci 93: 1945-1956.

2 WHO. 2003. WHO model list of essential medicines, 13th edn. Available from URL: http://www.who.int/medicines/organization/par/edl/expcom13/eml13_en.doc.

3 Verbeeck RK, Junginger HE, Midha KK, Shah VP, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: Chloroquine phosphate, chloroquine sulfate, and chloroquine hydrochloride. J Pharm Sci 94: 1389-1395.

4 Kortejärvi H, Yliperttula M, Dressman JB, Junginger HE, Midha KK, Shah VP, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: Ranitidine hydrochloride. J Pharm Sci 94: 1617-1625.

5 Potthast H, Dressman JB, Junginger HE, Midha KK, Oeser H, Shah VP, Vogelpoel H, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms: Ibuprofen. J Pharm Sci 94: 2121-2131.

6 Kalanzti L, Reppas C, Dressman JB, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky SA, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS): Acetaminophen (paracetamol). J Pharm Sci 95: 4-14.

7 Manzo HR, Olivera ME, Amidon GL, Dressman JB, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS): Amitryptiline hydrochloride. J Pharm Sci . Submitted for publication.

8 Somogyi A, Gugler R. 1983. Clinical pharmacokinetics of cimetidine. Clin Pharmacokinet 8: 463-495.

9 Martindale. The extra pharmacopoeia, 31st edn. London, UK: Royal Pharmaceutical Society.

10 The Merck Index, 13th edn. Rahway, New Jersey: Merck Research Laboratories.

11 Goodman & Gilman's. The Pharmacological Basis of Therapeutics, 10th edn. McGraw-Hill. Medical Publishing Division.

12 European Directorate for the Quality of Medicines. European Pharmacopoeia, 4th edn. Strasbourg, France: European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France.

13 USP 27-NF 22. 2004. The United States Pharmacopeia - The national formulary. Rockville MD, 20852: The United States Pharmacopeial Convention, Inc.

14 Shibata M, Kokubo H, Morimoto K, Morisaka K, Ishida T, Inoue M. 1983. X-ray structural studies and physicochemical properties of cimetidine polymorphism. J Pharm Sci 72: 1436-1442.

15 Kokubo H, Morimoto K, Ishida T, Inoue M, Morisaka K. 1987. Bioavailability and inhibitory effect for stress ulcer of cimetidine polymorphs in rats. Int J Pharm 35: 181-183.

16 Bueno WA, Sobrinho EG. 1995. Hydrogen bonds in the cimetidine molecule. Spectrochim Acta A Mol Biomol Spectrosc 51: 287-292.

17 Bauer-Brandl A. 1996. Polymorphic transitions of cimetidine during manufacture of solid dosage forms. Int J Pharm 140: 195-206.

18 Amidon GL, Lennernäs H, Shah VP, Crison JR. 1995. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 12: 413-420.

19 Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. 2004. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm 1: 85-96.

20 Avdeef A, Berger CM. 2001. pH-metric solubility: 3. Dissolution titration template method for solubility determination. Eur J Pharm Sci 14: 281-291.

21 Pedersen PV, Miller R. 1980. Pharmacokinetics and bioavailability of cimetidine in humans. J Pharm Sci 69: 394-398.

22 Bodemar G, Norlander B, Fransson L, Walan A. 1979. The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine - Studies in patients with peptic ulcer disease. Br J Clin Pharmacol 7: 23-31.

23 Russo J, Watson WA, Nelson EW, Schentag JJ. 1982. Cimetidine bioavailability after massive small bowel resection. Clin Pharm 1: 558-561.

24 Bodemar G, Norlander B, Walan A. 1981. Pharmacokinetics of cimetidine after single doses and during continuous treatment. Clin Pharmacokinet 6: 306-315.

25 Mummaneni V, Dressman JB. 1994. Intestinal uptake of cimetidine and ranitidine in rats. Pharm Res 11: 1599-1604.

26 Jantratid E, Prakongpan S, Amidon GL, Dressman JB. Feasibility of biowaiver extension to biopharmaceutics classification system class III drug products - Cimetidine. Clin Pharmacokinet . Accepted for publication.

27 Oberle RL, Amidon GL. 1987. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; An explanation for the double peak phenomenon. J Pharmacokinet Biopharm 15: 529-544.

28 Langguth P, Lee KM, Spahn-Langguth H, Amidon GL. 1994. Variable gastric emptying and discontinuities in drug absorption profiles: Dependence of rates and extent of cimetidine absorption on motility phase and pH. Biopharm Drug Dispos 15: 719-746.

29 Mummaneni V, Amidon GL, Dressman JB. 1995. Gastric pH influences the appearance of double peaks in the plasma concentration-time profiles of cimetidine after oral administration in dogs. Pharm Res 12: 780-786.

30 Takamatsu N, Welage LS, Hayashi Y, Yamamoto R, Barnett JL, Shah VP, Lesko LJ, Ramachandran C, Amidon GL. 2002. Variability in cimetidine absorption and plasma double peaks following oral

administration in the fasted state in humans: Correlation with antral gastric motility. Eur J Pharm Biopharm 53: 37-47.

31 Funaki T, Furuta S, Kaneniwa N. 1986. Discontinuous absorption property of cimetidine. Int J Pharm 31: 119-123.

32 Funaki T, Watari N, Furuta S, Kaneniwa N. 1988. Analysis of the absorption characteristics of cimetidine with the use of the multi-segment absorption model. Int J Pharm 43: 59-65.

33 Witcher JW, Boudinot FD. 1996. Applications and simulations of a discontinuous oral absorption pharmacokinetic model. Pharm Res 13: 1720-1724.

34 Zhou SY, Piyapolrungroj N, Pao L, Li C, Liu G, Zimmermann E, Fleisher D. 1999. Regulation of paracellular absorption of cimetidine and 5-aminosalicylate in rat intestine. Pharm Res 16: 1781-1785.

35 Gan LS, Yanni S, Thakker DR. 1998. Modulation of the tight junctions of the Caco-2 cell monolayers by H2-antagonists. Pharm Res 15: 53-57.

36 Collett A, Higgs NB, Sims E, Rowland M, Warhurst G. 1999. Modulation of the permeability of H2 receptor antagonists cimetidine and ranitidine by P-glycoprotein in rat intestine and the human colonic cell line Caco-2. J Pharmacol Exp Ther 288: 171-178.

37 Piyapolrungroj N, Zhou YS, Li C, Liu G, Zimmermann E, Fleisher D. 2000. Cimetidine absorption and elimination in rat small intestine. Drug Met Dispos 28: 65-72.

38 Hui YF, Kolars J, Hu Z, Fleisher D. 1994. Intestinal clearance of H2-antagonists. Biochem Pharmacol 48: 229-231.

39 Adkin DA, Davis SS, Sparrow RA, Huckle PD, Wilding IR. 1995. The effect of mannitol on the oral bioavailability of cimetidine. J Pharm Sci 84: 1405-1409.

40 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Office of Generic Drugs, Division of Labeling and Program Support. The inactive ingredient database. Available from URL: http://www.fda.gov/cder/iig/iigfaqWEB.htm.

41 Rege BD, Yu LX, Hussain AS, Polli JE. 2001. Effect of common excipients on Caco-2 transport of low-permeability drugs. J Pharm Sci 90: 1776-1786.

42 Basit AW, Podczeck F, Newton JM, Waddington WA, Ell PJ, Lacey LF. 2002. Influence of polyethylene glycol 400 on the gastrointestinal absorption of ranitidine. Pharm Res 19: 1368-1374.

43 Schulze JD, Waddington WA, Eli PJ, Parsons GE, Coffin MD, Basit AW. 2003. Concentration-dependent effects of polyethylene glycol 400 on gastrointestinal transit and drug absorption. Pharm Res 20: 1984-1988.

44 Koch KM, Parr AF, Tomlinson JJ, Sandefer EP, Digenis GA, Donn KH, Powell JR. 1993. Effect of sodium acid pyrophosphate on ranitidine bioavailability and gastrointestinal transit time. Pharm Res 10: 1027-1030.

45 Gleiter GH, Klotz U, Kuhlmann J, Blume H, Stanislaus F, Harder S, Paulus H, Poethko-Müller C, Holz-Slomczyk M. 1998. When are bioavailability studies required? A German proposal. J Clin Pharmacol 38: 904-911.

46 Committee for Proprietary Medicinal Products (CPMP). 2001. Note for guidance on the investigation of bioavailability and bioequivalence. Available from URL: http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf.

47 Bundesinstitut für Arzneimittel und Medizinprodukte. 2003. BundesAnzeiger. March 25: 5296.

48 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). 2000. Guidance for Industry: Waiver of in vivo bioavailability and bioequivalance studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Available from URL: http://www.fda.gov/cder/guidance/3618fnl.htm.

49 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). 1996. Bioequivalance report-Application number 74-890. Available from URL: http://www.fda.gov/cder/foi/anda/98/74-890 Cimetidine bioeqr.pdf.

50 Polli JE. 1997. In vitro-in vivo relationships of several immediate release tablets containing a low permeability drug. Adv Exp Med Biol 423: 191-198.

51 Cheng CL, Yu LX, Lee HL, Yang CY, Lue CS, Chou CH. 2004. Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: Bridging evidence for metformin immediate-release tablet. Eur J Pharm Sci 22: 297-304.

52 Blume HH, Schug BS. 1999. The biopharmaceutics classification system (BCS): Class III drugs - Better candidates for BA/BE waiver? Eur J Pharm Sci 9: 117-121.

53 Amidon GL. 1998. The rationale for a biopharmaceutics drug classification: Princeton, NJ, May 17, 1995. In: Capsugel symposia series: Biopharmaceutics drug classification and international drug regulation. Capsugel library, pp 179-194.

54 Takamatsu N, Kim ON, Welage LS, Idkaidek NM, Hayashi Y, Barnett J, Yamamoto R, Lipka E, Lennernäs H, Hussain A, Lesko L, Amidon GL. 2001. Human jejunal permeability of two polar drugs: Cimetidine and ranitidine. Pharm Res 18: 742-744.

55 Collett A, Sims E, Walker D, He YL, Ayrton J, Rowland M, Warhurst G. 1996. Comparison of HT29-18-C1 and Caco-2 cell lines as models for studying intestinal paracellular drug absorption. Pharm Res 13: 216-221.

56 Löbenberg R, Amidon GL. 2000. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm 50: 3-12.

57 Yee S. 1997. In vitro permeability across Caco-2 cells (colonic) can predict in vivo (small intestinal) absorption in man-fact or myth. Pharm Res 14: 763-766.

58 Pade V, Stavchansky S. 1997. Estimation of the relative contribution of the transcellular and paracellular pathway to the transport of passively absorbed drugs in the Caco-2 cell culture model. Pharm Res 14: 1210-1215.

59 Pade V, Stavchansky S. 1998. Link between drug absorption solubility and permeability measurements in Caco-2 cells. J Pharm Sci 87: 1604-1607.

60 Yazdanian M, Glynn SL, Wright JL, Hawi A. 1998. Correlating partitioning and caco-2 cell permeability of structurally diverse small molecular weight compounds. Pharm Res 15: 1490-1494.

61 Crespi CL, Fox L, Stocker P, Hu M, Steimel DT. 2000. Analysis of drug transport and metabolism in cell monolayer systems that have been modified by cytochrome P4503A4 cDNA-expression. Eur J Pharm Sci 12: 63-68.

62 Pontier C, Pachot J, Botham R, Lenfant B, Arnaud P. 2001. HT29-MTX and Caco-2/TC7 monolayers as predictive models for human intestinal absorption: Role of the mucus layer. J Pharm Sci 90: 1608-1619.

63 Sutcliffe FA, Riley SA, Kaser-Liard B, Turnberg LA, Rowland M. 1988. Absorption of drugs from human jejunum and ileum. Br J Clin Pharmacol 26: 206P-207P.

64 Artursson P, Palm K, Luthman K. 2001. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Adv Drug Deliv Rev 46: 27-43.

65 Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS. 2002. Biopharmaceutics classification system: The scientific basis for biowaiver extensions. Pharm Res 19: 921-925.

66 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). 1995. Guidance for Industry: Immediate release solid oral dosage forms. Scale-up and postapproval changes: Chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation. Available from URL: http://www.fda.gov/cder/guidance/cmc5.pdf.

67 Lindenberg M, Kopp S, Dressman JB. 2004. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm 58: 265-278.