COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Acetazolamide

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Received 16 July 2007; accepted 13 November 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21282

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 acetazolamide are reviewed. Acetazolamide's solubility and permeability characteristics according to the Biopharmaceutics Classification System (BCS), as well as its therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions and reported BE/bioavailability (BA) problems are taken into consideration. The available data on solubility, on oral absorption and permeability are not sufficiently conclusive to classify acetazolamide with certainty. Taking a conservative approach, no biowaiver is considered justified for the registration of new multisource drug products. However, SUPAC level 1 and level 2 postapproval changes and most EU Type I variations can be approved waiving *in vivo* BE studies. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:3691–3699, 2008

Keywords: acetazolamide; dissolution; absorption; Biopharmaceutics Classification System (BCS); permeability; regulatory science; solubility

INTRODUCTION

A monograph based on literature data is presented on acetazolamide, with respect to its biopharmaceutical properties and the risk of waiving *in vivo* bioequivalence (BE) testing in the approval of new immediate release (IR) solid

A project of the International Pharmaceutical Federation FIP, Group BCS, www.fip.org/bcs.

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

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Journal of Pharmaceutical Sciences, Vol. 97, 3691–3699 (2008)

oral dosage forms containing this active pharmaceutical ingredient (API), including both reformulated products and new multisource products. The purpose and scope of this series of monographs were discussed previously.[1] Briefly, the aim is to evaluate all pertinent data available from literature sources, to assess the risk of such a biowaiver (risk being defined as both the chance of arriving at an incorrect biowaiver decision, and an assessment of the likely impact of such an incorrect biowaiver decision on public health and individual patient risks) and recommend whether a biowaiver can be recommended or not. This systematic approach to recommend or advise against a biowaiver decision is referred in the recently published World Health Organization (WHO) Guideline.[2,3] It is pointed out that these monographs not simply apply this WHO Guideline, nor the FDA[4] and/or EMEA Guidance,[5] but also aim to serve as a critical validation of these regulatory documents. Monographs have been published on acetaminophen = paracetamol, amitriptyline hydrochloride, atenolol, ibuprofen, cimetidine, chloroquine-sulfate, -phosphate and -hydrochloride, ethambutol hydrochloride, isoniazid, ranitidine, prednisone, prednisolone, propanolol hydrochloride, and verapamil hydrochloride.[1,6–15] They are also available on-line at www.fip.org/bcs.

GENERAL CHARACTERISTICS

Name

INN name: acetazolamide, chemical name: *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide; N-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-acetamide; 5-acetamido-1,3,4-thiadiazole-2-sulfonamide. Its structure is shown in Figure 1.

Therapeutic Indication

Acetazolamide is an inhibitor of carbonic anhydrase and is used mainly in the management of glaucoma. It is also used in the treatment of various forms of epilepsy, to prevent or ameliorate the symptoms of acute high altitude sickness and in the promotion of diuresis in instances of abnormal fluid retention, for example, cardiac edema.[16]

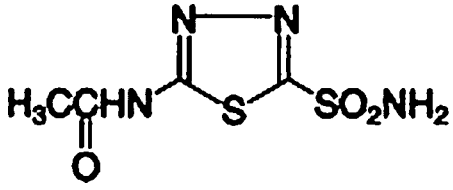

Figure 1. Structure of acetazolamide.

Therapeutic Index and Toxicity

Acetazolamide shows dose related side effects, the most common of which are diuresis, gastrointestinal (GI) symptoms including cramping, epigastric burning, nausea, and diarrhea and metabolic acidosis.[16,17] In rabbits, its therapeutic index was determined to be 2.7.[18] Although occurring rarely, several, often fatal, blood dyscrasias have been reported in patients taking acetazolamide,[16] including thrombocytopenic purpura,[19] pancytopenia,[20] and aplastic anaemia.[21]

CHEMICAL PROPERTIES

Salts, Stereoisomers, and Polymorphs

For acetazolamide, a sodium salt is known,[16] but has been used in parenteral dosage forms only, such as Acetazolamide for Injection USP.[22] There exists no stereoisomerism. Acetazolamide has two polymorphic forms (Forms I and II).[23] The solubility and dissolution rate of Form I at 37°C is about 1.1 times greater than those of Form II.[24] This small relative difference in solubility is not presumed to significantly affect the bioavailability (BA) of acetazolamide.[23]

Solubility

Acetazolamide is very slightly soluble in water; sparingly soluble in boiling water.[18] At 25°C, an aqueous solubility of 0.72 mg/mL was reported.[25] Between pH 1.68 and pH 8.17, solubilities of 0.8–2.8 mg/mL were reported.[25] Another source reports the solubility between pH 4 and pH 7 at 25°C to be approximately the same (0.8–1 mg/mL).[18] At 37°C, equilibrium solubilities of acetazolamide in pH 1.2 and pH 7.4 were reported to be 1.23 and 2.43 mg/mL, respectively.[26] At 25°C, between pH 1.68 and pH 8.17, solubilities of 1.26–2.79 mg/mL were reported.[27] Also, an aqueous solubility of 0.70 mg/mL was reported for acetazolamide.[28] These different values are tabulated in Table 1.

Table 1. Solubilities in Different Media and Corresponding Dose/Solubility (D/S) Ratio's for the 250 mg Tablet Strength*

Temperature (°C)	pH	Solubility (mg/mL)	D/S[a,b] (mL)	Refs.
25	1.68	1.26	198	27
25	3.19	1.08	231	27
25	4.01	1.17	214	27
25	4.98	0.80	313	27
25	5.27	0.87	287	27
25	5.47	0.82	305	27
25	6.06	0.89	281	27
25	6.85	1.01	248	27
25	8.17	2.79	90	27
25	Water	0.72	347	27
Not reported	Water	0.70	357	28
Not reported	Water	>0.1	<2500	16
Boiling	Water	>10	<25	16
37	7.2	4.13	61	25
37	1.2	1.23	203	26
37	7.4	2.43	103	26

*Highest strength on WHO Essential Medicines List and on DE, DK, FI, FR, NL, NO, SE, USA, and Argentina market.
[a] Critical limit: <250 mL.
[b] : Exceeds critical limit.

Partition Coefficient

A log P (n-octanol/water) value of −0.26 has been reported.[29] Machatha and Yalkowsky[30] reports an "Experimental value" of −0.26. Kasim et al.[31] calculated n-octanol/water partition coefficients using different fragmentation methods that were based on atomic contributions to lipophilicity. For acetazolamide, log P values of −1.13 ($C\log P^{®}$) and 0.14 (log P) were reported. Following the same methodology, log P values of 1.35 ($C\log P^{®}$) and 1.72 (log P) were reported for metoprolol. Other workers reported for acetazolamide computed log P values of −0.73 (log P), −0.26 (log P) and −1.25 ($C\log P^{®}$).[30]

pK_a

Acetazolamide is a weak acid with a pK_a value of 7.2.[18]

Dose and Dosage Forms Strengths

The WHO recommended dosage form strength is 250 mg.[32] In the USA, IR solid oral dosage forms of 125 and 250 mg have a marketing authorization (MA).[33] The same holds for many other countries, see Table 1. In Argentina, a MA for 250 mg exist.[34]

PHARMACOKINETIC PROPERTIES

Absorption and Permeability

Acetazolamide has been reported to be rapidly and almost completely absorbed from the GI tract (~100%),[18,35] reaching peak plasma concentrations approximately 1–3 h after oral administration.[18] However, neither of these references cites a primary literature source for the assertion that acetazolamide is well absorbed, raising questions about the validity of the statement. The Martindale reports acetazolamide to be fairly rapidly absorbed with peak plasma concentrations occurring about 2 h after oral doses.[16] The human first-order absorption rate constant is reported to be 0.821 h^{-1}.[17] The plasma concentrations of acetazolamide are proportional to dose,[17] fall in the therapeutic range, and the drug can be detected for 6–12 h after a single dose administration.[18] Food intake does not appear to influence absorption.[36] Usual therapeutic serum acetazolamide concentration range is 10–20 μg/mL (for glaucoma 4–5 μg/mL), with variations in response from

patient to patient.[37] Kunka and Mattocks[38] reported that acetazolamide follows a linear relationship between the AUC and the dose after intravenous bolus injections of ^{14}C-labeled acetazolamide, with doses ranging from 2 to 20 mg/kg, in rabbits. Alm et al.[39] determined the steady state plasma concentrations of acetazolamide in 40 patients after doses of 187.5, 375, 750, and 1000 mg. They found that mean plasma concentrations increased with increasing dosages but there were marked interindividual variations.

Crowe and Teoh[40] evaluated acetazolamide for its ability to be transported by P-glycoprotein (P-gp) through Caco-2 monolayers using apical (Ap) to basolateral (Bas), and Bas to Ap studies. The transport rates of acetazolamide in the Ap to Bas direction, using pH values of 7.4 or 6 in the Ap medium and 7.4 on the Bas side of the monolayers, was found to be 0.23×10^{-6} cm/s and 0.19×10^{-6} cm/s, respectively. The efflux rate was threefold higher than its uptake and P-gp inhibitors significantly reduced this. Thus, acetazolamide was shown to be a weak P-gp substrate. For carbamazepine, considered by the FDA Biowaiver guideline to be a *highly permeable* API,[40] the same study reported a transport rate of 55×10^{-6} cm/s, but used no internal standards as proposed by the FDA Biowaiver guideline.[40]

Kasim et al.[31] estimated permeabilities from correlations of experimentally determined human intestinal permeabilities with calculated values for log*P* and *C* log*P*®, using metoprolol as the reference compound. As the log*P* and *C* log*P*® values of acetazolamide were below the corresponding values for metoprolol, see above, these workers classified acetazolamide as not *highly permeable*.

Distribution, Metabolism, and Elimination

Acetazolamide is 70–90% protein-bound. The apparent volume of distribution is about 0.2 L/kg. It is widely distributed throughout the body, including the CNS. Acetazolamide is not metabolized and 90% of the administered dose is excreted unchanged in the urine within the first 24 h. This process involves both active tubular secretion and passive reabsorption. About 80% of the drug is excreted by tubular secretion of the anionic species. Its elimination half-life is about 4–8 h.[18,35]

DOSAGE FORM PERFORMANCE

Excipients and/or Manufacturing Variations

Yakatan et al.[41] evaluated the BA of five different lots of 250 mg acetazolamide tablets from a single manufacturer in 20 healthy volunteers. The composition of the tablets was not reported. The basic experimental design employed to determine relative BA of the five acetazolamide dosage forms was a balanced incomplete block design. Analysis of variance was utilized to determine whether the BA of the five tablets studied was different. The authors reported that no significant differences existed among the tablets for AUC and t_{max}, but two lots showed statistically higher C_{max} values than the other three lots, from which the authors concluded that lot-to-lot bio*in*equivalence existed.

Ellis et al. compared a generic acetazolamide tablet versus a brand-name acetazolamide tablet (Diamox®) in 12 patients.[4] Two tablet strengths were tested: 125 and 250 mg, using single-dose administration. Ocular hypotensive effects and serum levels were measured 1, 2, and 4 h after dosing. The brand-name tablet contained the excipients sodium starch glycolate, calcium phosphate, starch, povidone, magnesium stearate and microcrystalline cellulose; the generic tablet contained sodium starch glycolate, calcium phosphate, starch, povidone, and stearic acid as excipients. Following the administration of equal doses, the therapeutic effects of the generic tablet and brand-name tablet were not statistically different at any time point. Also, serum concentrations were similar for the generic and the brand-name tablet. Food intake did not influence the absorption from either formulation.

Straughn et al.[42] evaluated three tablet products containing 250 mg acetazolamide and a reference solution in 12 male healthy volunteers, in a crossover study using an enzymatic assay methodology for quantification. Of one tablet product two different lots were included in the study. The composition of the tablets was not reported. Using a Ewman-Keuls *a posteriori* statistical analysis, the authors concluded that there were no significant differences in AUC values among the four treatments, but that significant differences existed in C_{max} and t_{max} among the three tablet products.

The excipients used in the formulation of the core of the IR acetazolamide tablets marketed in Germany (DE),[43] Denmark (DK),[44] Finland (FI),[45]

France (FR),[46] The Netherlands (NL),[47] Norway (NO),[48] and Sweden (SE),[49] and the minimal and maximal amount of that excipients present per dosage unit in solid oral drug products with a MA in the USA[50] are summarized in Table 2. It can be inferred that these drug products successfully passed an *in vivo* BE study. In contrast to some other APIs, acetazolamide has not been exempted in DE,[51,52] nor is it still exempted from *in vivo* BE testing in NL for national applications.[53]

Dissolution and *In Vivo*/*In Vitro* Correlation

The USP 28 specification for acetazolamide tablets is not less than 75% (Q) of the labeled amount dissolved in 60 min in 900 mL 0.1 N HCl using the paddle apparatus operated at 100 rpm.[22]

Yakatan et al.[41] reported that the observed differences in C_{max} for five 250-mg acetazolamide tablets showed general trends for correlation with *in vitro* USP XIX dissolution tests, using stirring speeds at 50 and 100 rpm, in gastric fluid without pepsin and carbonate buffer pH 10, although the observed differences between the tablets did not appear to be of a sufficient magnitude to make the dissolution tests discriminatory except for one tablet, which proved to be the lowest disintegrating form tested. A better *in vivo*/*in vitro* correlation (IVIVC) was obtained with a rotating-filter-stationary basket apparatus. A much greater percentage difference was observed between the two tablets giving the highest blood levels than the other three tablets.

Straughn et al.[42] reported that differences in the rate of absorption of the three tablet products containing 250 mg acetazolamide showed a rank-order IVIVC at pH 1.5, using a basket apparatus operated at 50 rpm.

DISCUSSION

Solubility

An API is defined as *highly soluble* if it shows a dose/solubility (D/S) ratio of less than 250 mL at 37°C over a pH range of 1.2–6.8 (EU and WHO guidances) or 1–7.5 (FDA guidance).[4,5,54]

From the dataset at 37°C and taking 250 mg as the highest tablet strength, D/S values of

Table 2. Excipients Present in Acetazolamide IR Solid Oral drug Products with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO) and Sweden (SE), and the Minimal and maximal Amount of That Excipient Present Pro Dosage Unit in Solid Oral Drug Products with a 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)
Alginic acid	DE (1), FI (2), NL (3)	32–80
Calcium carbonate	FR (4)	8.6–350
Calcium hydrogen phosphate	DE (1, 5), DK (6), NL (3, 7), NO (8), SE (9)	104–850
Calcium stearate	FI (2)	0.7–43[a]
Cellulose	DE (1, 10), FI (2), NL (3)	4.6–1385[a]
Gelatin	DE (1), FI (2), FR (4), NL (3)	1–756[a]
Glycerol	DE (1), NL (3)	0.14–198[b]
Hydroxypropylcellulose	FI (2)	4–132
Lactose	FI (2)	23–1020[a]
Magnesium stearate	DE (1, 5, 10), DK (6), FR (4), NL (3, 7), NO (8), SE (9)	0.15–401[a]
Povidone	DE (1,5), DK (6), NL (3, 7), NO (8), SE (9)	0.17–75
Silica	DE (10), FI (2)	0.65–99
Sodium starch glycolate	DE (5, 10), DK (6), NL (7), NO (8), SE (9)	2–876[a]
Starch	DE (1, 5, 10), DK (6), FR (4), NL (3, 7), NO (8), SE (9)	2.1–1135
Starch, pregelatinized	FI (2)	6.6–600
Talc	DE (1), FI (2), NL (3)	0.26–220[a]

1, Glaupax® Tabletten (Mono); 2, Ödemin 250 mg—abletti; 3, Acetazolamide Sandoz 250, Tabletten 250 mg; 4, DIAMOX 250 mg cp séc; 5, Diamox® Tabletten (Mono); 6, Diamox, tabletter 125 mg/−250 mg; 7, Diamox, Tabletten 250 mg; 8, Diamox 250 mg tablet; 9, Diamox 125 mg/−250 mg tabletter; 10, Diuramid Tabletten (Mono).

[a]The upper range value reported is unusual high for solid oral dosage forms and the authors doubt on its correctness.

[b]The authors have doubt on the correctness of these data. Such amounts are normally present in a soft gelatin capsules, but not in capsules, as indicated by FDA Inactive Ingredients Database.

203 mL at pH 1.2 and 103 mL at pH 7.4 at 37°C, respectively, are calculated, see Table 1. However, no solubility data at 37°C are reported in the middle pH range (pH 2–6). The relatively low increase in solubility at pH 1.2 at 37°C compared to 25°C suggests that D/S in the middle pH range might fall outside the cut-off limit of 250 mL at 37°C. The D/S ratio of 103 mL obtained at pH 7.4 is eligible for a classification as *highly soluble* according to the FDA, but the highest pH indicated by the EMEA guideline and the WHO is pH 6.8, not pH 7.4. Under the latter regulations, acetazolamide cannot be definitively classified as *highly soluble*.

Absorption and Permeability

For drug transport in Caco-2 monolayers, a cutoff point for *highly permeable* APIs of $P_{app} = 10^{-5}$ cm/s, was proposed, which should ensure a fraction dose absorbed higher than 95%.[54] Other workers proposed a cutoff limit of P_{app} of 2×10^{-6} cm/s in Caco-2 cells for expecting 100% absorption.[55] Cut-off limits of P_{app} from 2×10^{-6} cm/s to 10^{-5} cm/s as a boundary of *highly permeable* were proposed by Rinaki et al.[56] The P_{app} of acetazolamide in Caco-2 cells, being in the range of 0.2×10^{-6} cm/s, is a factor of 10–50 below these boundary values. However, Caco-2 permeability determinations are known to display tremendous interlaboratory variability.[54]

From correlations from calculated values for $\log P$ and $C \log P$, using metoprolol as the reference compound, acetazolamide was classified as not *highly permeable*. However, correlations of $\log P$ values with human intestinal permeability showed false positives and negative results.[31]

More important is the fraction dose absorbed in humans, which is the basis of the permeability classification. In the FDA Guidances, an API is *highly permeable* when the fraction of dose absorbed from an orally administered dose is 90% or more.[4] The recently revised WHO Guidelines sets a lower limit of 85%.[2] The EU Note for Guidance does not define a limit, but states: "linear and complete absorption indicating high permeability reduces the possibility of IR dosage forms influencing the BA."[5] However, the fraction of dose absorbed, reported to be ~100%,[18,35] is not reliable, since no primary studies were cited. Thus, data on the oral absorption and permeability for this API are not sufficient to conclude whether acetazolamide is *highly permeable* or not.

BCS Classification

Kasim et al.[31] classified acetazolamide as BCS Class IV. However, their classification is based on solubility data in water, presumably at room temperature and calculated partition coefficients, not the solubility in different buffer systems at 37°C and the fraction of dose absorbed.

Lindenberg et al.[57] report acetazolamide to be an API for which complete solubility and/or permeability data are lacking, also tentatively assigning this API to BCS Class IV.

Wu and Benet[58] classified acetazolamide as Class IV in their Biopharmaceutics Drug Disposition Classification System (BDDCS), a system using the disposition characteristics of an API as estimate for its GI permeability.

We conclude that the available data on solubility, on oral absorption and permeability are not sufficiently conclusive to classify this API with sufficient certainty.

Risks of Bio*in*equivalence Caused by Excipients and/or Manufacturing

While no studies reported bio*in*equivalence with respect to AUC, two studies reported bio*in*equivalence with respect to C_{max} and/or t_{max}. So, bio*in*equivalence of some type has been reported in most, if not all, studies carried out.

Surrogate Techniques for *In Vivo* BE Testing

The studies of Yakatan and Straughn suggest that differences in the rate of absorption can be correlated with *in vitro* dissolution in pH 1.5. However, the methods used did not coincide with the dissolution test methods developed for biowaiver purposes, as described in the Guidances of FDA, EMEA, and WHO.[2,4,5]

Up to now, there exists no *in vitro* tests capable of detecting bio*in*equivalence caused by differences in GI permeability and GI transit time. In previous monographs, these risks were minimized by accepting for a biowaiver only test drug product containing excipients also present in drug products having a MA in a number of countries, as it was assumed that these registrated drug products had successfully passed an *in vivo* BE study.

Patient's Risks Associated with Bio*in*equivalence

The therapeutic plasma concentration for acetazolamide ranges from 10–20 μg/mL (for glaucoma

4–5 μg/mL), while its toxic plasma concentration ranges from 25–30 μg/mL.[37] According to the FDA definition[59] for narrow therapeutic index, acetazolamide is a narrow therapeutic index drug, since there is a less than twofold difference between the highest reported toxic concentration (30 μg/mL) and the highest reported therapeutic plasma concentration (20 μg/mL).

Also, it is to be considered that the rate of onset of action may be clinically relevant for acetazolamide, since acetazolamide is used against acute high ocular pressure to prevent damage of the optic nerve and hence bio*in*equivalence with respect to C_{max} may be clinically relevant.

On the other hand, the Pan American Health Organization (PAHO) classified acetazolamide as a low health-risk drug, in view of the margin between the nontoxic maximum and effective minimum concentrations and the adverse effects, indicating a low probability of appearance of a minor complication of the disease and/or mild adverse reactions arising from plasma concentrations outside the therapeutic window of the drug.[60]

The severe, often fatal, blood dyscrasias reported in patients taking acetazolamide are not related to dose and/or absorption rate and hence likely not be related to bio*in*equivalent drug products.

CONCLUSION

Taking a conservative approach, no biowaiver is considered justified for the approval of new multisource drug products.

It is not concluded that biowaiving is always unjustified. Postapproval changes in approved drug products, such a change in the manufacturing formula, in the manufacturing process, in manufacturing sites and/or equipment necessitate demonstration of BE. If such changes are small, such changes are approvable without an *in vivo* BE study. The FDA describes such post approval changes as SUPAC level 1 and level 2.[61] The EU has a comparable system.[62] When an approved acetazolamide IR drug product falls into such category, waving of an *in vivo* BE study is justified from a scientific and regulatory point of view. However, this holds for small changes to already approved drug products only. For the approval of new multisource drug products, waving of an *in vivo* BE study is not justified from a scientific and regulatory point of view.

ACKNOWLEDGMENTS

Kik Groot, RIVM, is acknowledged for producing Table 2.

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, 2006. Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability. Technical Report Series, No937, 40th Report, Annex 7 http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf4.
3. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Technical Report Series, No937, 40th Report, Annex 8 http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf.
4. FDA. 2000. Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solidoral dosage forms based on a Biopharmaceutics Classification System. USA: US Food and Drug Administration, Center for Drug Evaluation and Research http://www.fda.gov/cder/guidance/3618fnl.pdf.
5. CPMP, 2001. Note for guidance on the investigation of bioavailability and bioequivalence. http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf.
6. 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.
7. 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.
8. 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.
9. 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.
10. Manzo HR, Olivera ME, Amidon GL, Dressman JB, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS): Amitryptiline hydrochloride. J Pharm Sci 95:966–973.
11. Jantratid E, Prakongpan S, Dressman JB, Amidon GL, Junginger HE, Midha KK, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms: Cimetidine. J Pharm Sci 95:974–984.
12. Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms: Isoniazid. J Pharm Sci 96:522–531.
13. Vogt M, Derendorf H, Kramer J, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Prednisolone. J Pharm Sci 96:27–37.
14. Vogt M, Derendorf H, Kramer J, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Prednisone. J Pharm Sci 96:1480–1489.
15. Becker C, Dressman JB, Kopp S, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky S, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Ethambutol dihydrochloride. J Pharm Sci (accepted for publication).
16. Sweetman S, editor. 2005. Martindale: The complete drug reference. Electronic version. London, UK; Greenwood Village, Colorado: Pharmaceutical Press, Thomson. MICROMEDEX.
17. Yano I, Takayama A, Takano M, Inatani M, Tanihara H, Ogura Y, Honda Y, Inui K. 1998. Pharmacokinetics and pharmacodynamics of acetazolamide in patients with transient intraocular pressure elevation. Eur J Clin Pharmacol 54:63–68.
18. Parasrampuria J. 1993. In: Brittain HG, editor. Analytical profiles of drug substances and excipients. Vol. 22 San Diego, London: Academic Press. pp 3–32.
19. Corbett JT. 1985. Acetazolamide and purpura. Br Med J 1:1122–1123.
20. Englund GW. 1969. Fatal pancytopenia and acetazolamide therapy. JAMA 210:2282.
21. Niven BI, Manoharan A. 1985. Acetazolamide-induced anaemia. Med J 1:1500–1505.
22. USP 28-NF 23. 2005. The United States Pharmacopeia—The National Formulary. Rockville MD2085: The United States Pharmacopeial Convention, Inc.
23. Griesser UJ, Burger A, Mereiter K. 1997. The polymorphic drug substances of the European Pharmacopoeia. Part 9. Physicochemical properties and crystal structure of acetazolamide crystal forms. J Pharm Sci 86:352–358.
24. Pudipeddi M, Serajuddin ATM. 2005. Trends in solubility of polymorphs. J Pharm Sci 94:929–939.
25. Duffel MW, Ing IS, Segarra TM, Dixson JA, Barfknecht CF, Schoenwald RD. 1986. N-Substituted sulfonamide carbonic anhydrase inhibitors with topical effects on intraocular pressure. J Med Chem 29:1488–1494.
26. Haznedar S, Dortunç B. 2004. Preparation and in vitro evaluation of Eudragit microspheres containing acetazolamide. Int J Pharm 269:131–240.
27. Parasrampuria J, Das Gupta V. 1990. Development of oral liquid dosage forms of acetazolamide. J Pharm Sci 79:835–836.
28. BP. 1980. Pharm. Eur. 4.00 Kommentar (German).
29. Remko M, von der Lieth C-W. 2004. Theoretical study of gas-phase acidity, pKa, lipophilicity, and solubility of some biologically active sulfonamides. Bioorg Med Chem 12:5395–5403.
30. Machatha SG, Yalkowsky SH. 2005. Comparison of the octanol/water partition coefficients calculated by ClogP®, ACDlogP and Kow Win® to experimentally determined values. Int J Pharm 294:185–192.
31. 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.
32. WHO, Model List of Essential Medicines 13th edn. Available from URL www.who.int/medicines/organization/par/edl/expcom13/eml13_en.doc
33. FDA/Center for Drug Evaluation and Research Office of Generic Drugs. Available from URL http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm.
34. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica de la República Argentina. Available from URL http://www.anmat.gov.ar.
35. Ritschel WA, Paulos C, Arancibia A, Agrawal MA, Wetzelsberger KM, Lücker PW. 1998. Pharmacokinetics of acetazolamide in healthy volunteers after short- and long-term exposure to high altitude. J Clin Pharmacol 38:533–539.
36. Ellis PP, Price PK, Kelmenson R, Rendi MA. 1982. Effectiveness of generic acetazolamide. Arch Ophthalmol 100:1920–1922.
37. Schulz M, Schmoldt A. 2003. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 58:447–473.
38. Kunka RL, Mattocks AM. 1979. Nonlinear model for acetazolamide. J Pharm Sci 68:342–346.

39. Alm A, Berggren L, Hartving P, Roosdorp M. 1982. Monitoring acetazolamide treatment. Acta Ophthalmol (Copenh) 60:24–34.
40. Crowe A, Teoh YK. 2006. Limited P-glycoprotein mediated efflux for anti-epileptic drugs. J Drug Target 14:291–300.
41. Yakatan GJ, Frome EL, Leonard RG, Shah AC, Doluisio JT. 1978. Bioavailability of acetazolamide tablets. J Pharm Sci 67:252–256.
42. Straughn AB, Gollamudi R, Meyer MC. 1982. Relative bioavailability of acetazolamide tablets. Biopharm Drug Dispos 3:75–82.
43. Gleiter CH, Gundert-Remy U. 1994. Bioinequivaleance and drug toxicity. How great is the problem and what can be done? Drug Saf 11: 1–6.
44. RoteListe®. Arzneimittelsverzeichnis für Deutschland www.rote-liste.de (assessed 24-10-2006).
45. Lægemiddelstyrelsen www.dkma.dk (assessed 24-10-2006).
46. Lääkelaitos www.nam.fi (assessed 24-10-2006).
47. L'information de référence sur les produits de santé www.vidal.fr (assessed 24-10-2006).
48. Het College ter Beoordeling van Geneesmiddelen www.cbg-meb.nl (assessed 24-10-2006).
49. Statens lækjemiddelverk www.legemiddelverket.no (assessed 24-10-2006).
50. FDA, Inactive Ingredient Database http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose (version date 03-10-2006).
51. Läkemedelsverket www. lakemedelsverket.se (assessed 24-10-2006).
52. Gleiter CH, Klotz U, Kuhlmann J, Blume H, Stanislaus F, Harder S, Paulus H, Poethko-Muller C, Holz-Slomczyk M. 1998. When are bioavailability studies required? A German proposal. J Clin Pharmacol 38:904–911.
53. College ter Beoordeling van Geneesmiddelen. Lijst vrijstelling bio-equivalentieonderzoek (positieve lijst) (List of APIs exempted from demonstration in vivo of bioequivalence when formulated in IR solid oral dosage forms) http://www.cbg-meb.nl/nl/reghoudr/vrij.htm.
54. Artursson P, Palm K, Luthman K. 2001. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Adv Drug Del Rev 46:27–43.
55. Gres M-C, Julian B, Bourre M, Meunier V, Roques C, Berger M, Boulenc X, Berger Y, Fabre G. 1998. Correlation between oral drug absorption in humans and apparent drug permeability in TC-7 cells, a human epithelial intestinal cell line: Comparison with the parental Caco-2 cell line. Pharm Res 15:726–733.
56. Rinaki E, Valsami G, Macheras P. 2003. Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio. Pharm Res 20:1917–1925.
57. 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 Pham Biopharm 58:265–278.
58. Wu C-Y, Benet LZ. 2005. Predicting drug disposition via application of BCS: Transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res 22:11–23.
59. FDA, Code of Federal Regulations. Title 21, Part 320: Bioavailability and Bioequivalence requirements. Section 320.33. 2003 www.accessdata.fda.gov.
60. PAHO, Science based criteria for bioequivalence in vivo and in vitro, biowaivers, and strategic framework for implementation www.paho.org/english/ad/ths/ev/be-doct-draft-eng.pdf.
61. FDA, 2005. 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. (SUPAC-IR). www.fda.gov/cder/guidance/supac.htm.
62. European Commission, 2006. Guideline on Dossier requirements for Type IA and Type IB. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/var_type_1a1b_guideline_06-2006.pdf.