COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Acetazolamide

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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.

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.
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.\(^16\)

### 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.\(^25\)

#### 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.

![Figure 1. Structure of acetazolamide.](image-url)
 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 \(-1.13\) (\( C \log P^{E} \)) and \(-0.14\) (log \( P \)) were reported. Following the same methodology, log \( P \) values of \(-1.35\) (\( C \log P^{E} \)) 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 \(-1.25\) (\( C \log P^{E} \)).\(^{30}\)

\( pK_a \)

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 Martin-dale 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

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

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>pH</th>
<th>Solubility (mg/mL)</th>
<th>D/S(^{a,b}) (mL)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1.68</td>
<td>1.26</td>
<td>198</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>3.19</td>
<td>1.08</td>
<td>231</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>4.01</td>
<td>1.17</td>
<td>214</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>4.98</td>
<td>0.80</td>
<td>313(^{n})</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>5.27</td>
<td>0.87</td>
<td>287(^{n})</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>5.47</td>
<td>0.82</td>
<td>305(^{n})</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>6.06</td>
<td>0.89</td>
<td>281(^{n})</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>6.85</td>
<td>1.01</td>
<td>248(^{n})</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>8.17</td>
<td>2.79</td>
<td>90</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>Water</td>
<td>0.72</td>
<td>347(^{n})</td>
<td>27</td>
</tr>
<tr>
<td>Not reported</td>
<td>Water</td>
<td>&gt;0.1</td>
<td>&lt;2500(^{n})</td>
<td>16</td>
</tr>
<tr>
<td>Boiling</td>
<td>Water</td>
<td>&gt;10</td>
<td>61</td>
<td>25</td>
</tr>
<tr>
<td>37</td>
<td>7.2</td>
<td>4.13</td>
<td>203</td>
<td>26</td>
</tr>
<tr>
<td>37</td>
<td>1.2</td>
<td>1.23</td>
<td>103</td>
<td>26</td>
</tr>
</tbody>
</table>

\(^{a}\)Highest strength on WHO Essential Medicines List and on DE, DK, FI, FR, NL, NO, SE, USA, and Argentina market.

\(^{b}\)Critical limit: <250 mL.

\(^{n}\)Exceeds critical limit.
patient to patient. Kunka and Mattocks\textsuperscript{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.\textsuperscript{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\textsuperscript{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 $0.23 \times 10^{-6}$ cm/s and $0.19 \times 10^{-6}$ 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,\textsuperscript{40} the same study reported a transport rate of $55 \times 10^{-6}$ cm/s, but used no internal standards as proposed by the FDA Biowaiver guideline.\textsuperscript{40}

Kasim et al.\textsuperscript{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.\textsuperscript{18,35}

**DOSE FORM PERFORMANCE**

**Excipients and/or Manufacturing Variations**

Yakatan et al.\textsuperscript{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 $t_{\text{max}}$, but two lots showed statistically higher $C_{\text{max}}$ values than the other three lots, from which the authors concluded that lot-to-lot bioinequivalence existed.

Ellis et al. compared a generic acetazolamide tablet versus a brand-name acetazolamide tablet (Diamox\textsuperscript{®}) in 12 patients.\textsuperscript{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.\textsuperscript{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 $C_{\text{max}}$ and $t_{\text{max}}$ among the three tablet products.

The excipients used in the formulation of the core of the IR acetazolamide tablets marketed in Germany (DE),\textsuperscript{43} Denmark (DK),\textsuperscript{44} Finland (FI),\textsuperscript{45}
France (FR), The Netherlands (NL), Norway (NO), and Sweden (SE), and the minimal and maximal amount of that excipients present per dosage unit in solid oral drug products with a MA in the USA 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, nor is it still exempted from in vivo BE testing in NL for national applications.

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.

Yakatan et al. reported that the observed differences in $C_{\text{max}}$ 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. 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).

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

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Drug Products Containing That Excipient With a MA Granted by the Named Country</th>
<th>Range Present in Solid Oral Dosage Forms With a MA in the USA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginic acid</td>
<td>DE (1), FI (2), NL (3)</td>
<td>32–80</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>FR (4)</td>
<td>8.6–350</td>
</tr>
<tr>
<td>Calcium hydrogen phosphate</td>
<td>DE (1, 5), DK (6), NL (3, 7), NO (8), SE (9)</td>
<td>104–850</td>
</tr>
<tr>
<td>Calcium stearate</td>
<td>FI (2)</td>
<td>0.7–43&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cellulose</td>
<td>DE (1, 10), FI (2), NL (3)</td>
<td>4.6–1385&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gelatin</td>
<td>DE (1), FI (2), FR (4), NL (3)</td>
<td>1–756&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glycerol</td>
<td>DE (1), NL (3)</td>
<td>0.14–198&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>FI (2)</td>
<td>4–132</td>
</tr>
<tr>
<td>Lactose</td>
<td>FI (2)</td>
<td>23–1020&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>DE (1, 5, 10), DK (6), FR (4), NL (3, 7), NO (8), SE (9)</td>
<td>0.15–401&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Povidone</td>
<td>DE (1, 5), DK (6), NL (3, 7), NO (8), SE (9)</td>
<td>0.17–75</td>
</tr>
<tr>
<td>Silica</td>
<td>DE (10), FI (2)</td>
<td>0.65–99</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>DE (5, 10), DK (6), NL (7), NO (8), SE (9)</td>
<td>2–876&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Starch</td>
<td>DE (1, 5, 10), DK (6), FR (4), NL (3, 7), NO (8), SE (9)</td>
<td>2.1–1135</td>
</tr>
<tr>
<td>Starch, pregelatinized</td>
<td>FI (2)</td>
<td>6.6–600</td>
</tr>
<tr>
<td>Talc</td>
<td>DE (1), FI (2), NL (3)</td>
<td>0.26–220&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The upper range value reported is unusual high for solid oral dosage forms and the authors doubt on its correctness.
<sup>b</sup>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 $P_{\text{app}} = 10^{-5}$ cm/s, was proposed, which should ensure a fraction dose absorbed higher than 95%. Other workers proposed a cutoff limit of $P_{\text{app}} = 2 \times 10^{-6}$ cm/s in Caco-2 cells for expecting 100% absorption. Cut-off limits of $P_{\text{app}}$ from $2 \times 10^{-6}$ cm/s to $10^{-5}$ cm/s as a boundary of highly permeable were proposed by Rinaki et al. The $P_{\text{app}}$ of acetazolamide in Caco-2 cells, being in the range of $0.2 \times 10^{-6}$ cm/s, is a factor of 10–50 below these boundary values. However, Caco-2 permeability determinations are known to display tremendous interlaboratory variability.

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.

More important is the fraction dose absorbed in humans, which is the basis of the permeability classification. In the FDA Guidelines, an API is highly permeable when the fraction of dose absorbed from an orally administered dose is 90% or more. The recently revised WHO Guidelines sets a lower limit of 85%. 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.” However, the fraction of dose absorbed, reported to be ~100%, 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. 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. 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 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 Bioequivalence Caused by Excipients and/or Manufacturing

While no studies reported bioequivalence with respect to AUC, two studies reported bioequivalence with respect to $C_{\text{max}}$ and/or $t_{\text{max}}$. So, bioequivalence 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 bio-waiver purposes, as described in the Guidelines of FDA, EMEA, and WHO.

Up to now, there exists no in vitro tests capable of detecting bioequivalence caused by differences in GI permeability and GI transit time. In previous monographs, these risks were minimized by accepting for a bio waiver 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 regis trated drug products had successfully passed an in vivo BE study.

Patient’s Risks Associated with Bioequivalence

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. According to the FDA definition, for narrow therapeutic index, acetazolamide is a narrow therapeutic index drug, since acetazolamide is used against acute high ocular pressure to prevent damage of the optic nerve and hence bioinequivalence with respect to C$_{\text{max}}$ may be clinically relevant.

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 bioinequivalence with respect to C$_{\text{max}}$ 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.

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 bioinequivalent 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. 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

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