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 levofloxacin as the only active pharmaceutical ingredient (API) are reviewed. According to the current Biopharmaceutics Classification System, levofloxacin can be assigned to Class I. No problems with BE of IR levofloxacin formulations containing different excipients and produced by different manufacturing methods have been reported and hence the risk of bioinequivalence caused by these factors appears to be low. In addition, levofloxacin has a wide therapeutic index. On the basis of this evidence, a biowaiver is recommended for IR solid oral dosage forms containing levofloxacin as the single API provided that (a) the test product contains only excipients present in IR levofloxacin drug products that have been approved in International Conference on Harmonization (ICH) or associated countries and which have the same dosage form; (b) both the test and comparator dosage form are “very rapidly dissolving” or “rapidly dissolving” with similarity of the dissolution profiles demonstrated at pH 1.2, 4.5, and 6.8; and (c) if the test product contains polysorbates, it should be both qualitatively and quantitatively identical to its comparator in terms of polysorbate content. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:1628–1636, 2011

Keywords: levofloxacin; absorption; Biopharmaceutics Classification System (BCS); permeability; regulatory science; solubility
levofloxacin as the only active pharmaceutical ingredient (API) and not to combination products. The purpose and scope of this series of monographs have been previously discussed. Summarized in few words, the aim is to evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of the decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver approval is advisable or not. This systematic approach to recommend or advise against a biowaiver decision is referred to in the recently published World Health Organization (WHO) guideline. These monographs do not intend to simply apply the WHO, United States Food and Drug Administration (FDA), and/or European Medicine Agency (EMA) Guidance, but aim also as a critical evaluation of these and other countries’ regulatory documents. Biowaiver monographs have already been published for several APIs, also available online at www.fip.org/bcs.

Experimental

Literature data were obtained from Web of Science, PubMed, and Micromedex databases up to December 2009. The keywords used for searching were levofloxacin, intestine absorption, linear absorption, absolute bioavailability (BA), BE, log $P$, solubility, permeability, and lipophilicity. Information was also obtained from regulatory documents published by the WHO, the FDA, and the EMA. Biowaiver monographs have already been published for several APIs, also available online at www.fip.org/bcs.

GENERAL CHARACTERISTICS

Levofloxacinum/Levofloxacin (INN), (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. The molecule exists as a zwitterion at the pH conditions in the small intestine. The commercially available drug substance is the hemihydrate with the empirical formula $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2}H_2O$ and containing 97.6% levofloxacin by mass. Its structure is shown in Figure 1.

Stereochernistry

Levofloxacin is the S(-) isomer of the racemic drug substance ofloxacin; it is significantly more active against bacterial pathogens than R(+)-ofloxacin.

Therapeutic Indication

Levofloxacin has a broad spectrum of in vitro activity against Gram-positive and Gram-negative bacteria. In Brazil, its labeled indications include treatment of adults (≥ 18 years old) with mild, moderate, and severe infections caused by susceptible strains such as upper and lower respiratory tract infection, infection of skin and/or subcutaneous tissue, urinary tract infection, acute pyelonephritis, osteomyelitis, related septicemia/bacteremia, intra-abdominal infections, prostatitis, and nosocomial pneumonia. In the United States (US) in addition to the above-mentioned indications, levofloxacin has been approved to treat infection caused by inhaled anthrax (prophylaxis or postexposure). Also, according to the 16th edition of WHO’s Essential Medicines List, levofloxacin may be used as an alternative to ofloxacin in the treatment of multidrug resistant tuberculosis.

Therapeutic Index and Toxicity

Levofloxacin exhibits a low potential for acute toxicity. The median lethal dose (LD$_{50}$) values were around 1800 mg/kg for mice, 1500 mg/kg for rats, and more than 250 mg/kg in female monkeys. Generally, its serum and tissue levels do not require routine monitoring. Depending on the indication, the dosage regimen can vary from 250 mg daily for 3 days to 500 mg daily for 28 days. Daily doses can be as high as 750 mg. The most common adverse reactions (≥ 3%) in humans are nausea, headache, diarrhea, insomnia, constipation, and dizziness. Dysglycemia and liver disorders in association with levofloxacin have been reported in the literature. Disturbances of blood glucose levels are labeled in the product monograph. As with other quinolones, disturbances of blood glucose, including symptomatic hyper and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. Postmarketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients with 65 years old or older and most were not associated with hypersensitivity.

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons

Figure 1. Structure of levofloxacin hemihydrate (Molecular weight = 370.38).
resulting in paresthesias, hypoesthesias, dysesthesias, weakness, and infrequent cases of arrhythmia have been reported. Clinical pharmacologic studies performed with supratherapeutic doses also showed an increase in QT intervals. The risk of developing levofloxacin-associated tendinitis and tendon rupture is further increased in older patients (usually defined as over 60 years old), in those taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. In this case the therapy should be discontinued.

CHEMICAL PROPERTIES

Solubility

The solubility of levofloxacin in water is around 25 mg/mL (temperature not reported, presumably ambient). Levofloxacin shows pH-dependent solubility. Over the pH range of 2–5, the solubility is essentially constant, approximately 200 mg/mL; above pH 5.5, the solubility increases to a maximum value of approximately 300 mg/mL at about pH 6.5, whereas above pH 6.5, the solubility decreases and reaches its minimum value of approximately 30 mg/mL at about pH 7.5. All these data were taken at 20°C.

Polymorphs

Three polymorphic forms (anhydrous α, β, γ) and two pseudopolymorphic forms (hemihydrate and monohydrate) of levofloxacin occurs, depending on the temperature used in the manufacturing process. Polymorph-dependent BA has not been reported.

Partition Coefficient (log P)

Log P and log D (pH 7) values of 1.49 ± 0.79 and −1.35, respectively, were calculated for levofloxacin by using the software Solaris v4.67 (ACD/Labs, Toronto, Canada). The temperature was not reported, presumably ambient. Other authors reported a log P of −0.40 without reporting the experimental conditions.

PKa

Levofloxacin is a zwitterion at physiological pH, possessing a carboxylic group with pKa = 5.5, a piperazinyl group with pKa = 8.0 and another proton-accepting function with pKa = 6.8 ± 0.3.

Available Dosage Form Strengths

The WHO Essential Medicines List includes levofloxacin as an alternative for ofloxacin, based on availability and programme considerations; however, no dosage form and dosage form strengths are given. Other WHO documents report 500 mg and 250 mg, 500 mg and 750 mg tablets, respectively. Commercially available are tablets of 250, 500, and 750 mg (Table 1).

PHARMACOKINETIC PROPERTIES

Absorption and BA

The pharmacokinetics of levofloxacin is well described by a linear two-compartment open model with first-order elimination. Plasma concentrations in healthy volunteers reach a mean peak drug plasma concentration (Cmax) of approximately 2.8 and 5.2 mg/L within 1–2 h after oral administration of levofloxacin 250 and 500 mg tablets, respectively. The BA of oral levofloxacin is very rapid and approaches 100% and is little affected by administration with food. Frick et al. calculated the in vivo dissolution of levofloxacin tablets by numerical deconvolution from the plasma concentrations measured in a BA study comparing intravenous infusion versus oral administration, and estimated that more than 80% of the oral dose had been absorbed after 1 h, which was interpreted as indicating that gastric emptying controls the absorption rate. Single oral doses of levofloxacin from 50 to 1000 mg produce a mean Cmax and area under the plasma concentration–time curve (AUC) from approximately 0.6 to 9.4 mg/L and 4.7 to 108 mg·h/L, respectively, both increasing linearly in a dose-proportional fashion. Although chelation of levofloxacin by divalent cations can occur, it is less marked than with other fluoroquinolones. The BA of oral levofloxacin (100 mg) was reduced significantly during concomitant administration of aluminum hydroxide 1 g (by 44%), magnesium oxide 500 mg (by 22%), and ferrous sulfate 160 mg (by 19%).

Permeability

The log P values reported differ widely. However, as human BA data are available, partition coefficient data can be disregarded for the permeability classification of levofloxacin. Because levofloxacin is a zwitterionic compound, passive diffusion may not fully explain the high intestinal absorption. In Caco-2 cells the apical influx clearance value at pH 6 was much greater than the basolateral influx clearance value, suggesting uptake across the apical membrane in Caco-2 cells to be mediated by a specific transport system. A good correlation was found between the expression levels of organic anion transporting polypeptide 1A2 (OATP 1A2) and levofloxacin influx clearance in Caco-2 cells. The in vitro permeability of levofloxacin was evaluated using a suitable Caco-2 assay according to the criteria in the Biopharmaceutics Classification System (BCS) Guidance. Metoprolol, labetalol, and atenolol served as high
Table 1. Excipients<sup>a</sup> Present in Levofloxacin IR Solid Oral Drug Products with a Marketing Authorization (MA)<sup>b</sup> in a Number of Countries<sup>c</sup> and the Minimal and Maximal Amount of that Excipient Present Per Dosage Unit in Solid Oral Drug Products with a MA in the US

<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 US (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose</td>
<td>BR (1,2) CA (3–11) CZ (12–15) DE (16) DK (17–19) ES (20–29) FI (30,31) FR (32,33) HU (34–36) IE (37–40) IL (41) NL (42–48) SE (49–51) UK (52)</td>
<td>4.6–1385&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Copovidone</td>
<td>CA (9–11) DK (17,19) ES (21) FI (30) HU (35) IE (37) NL (68,69)</td>
<td>357–854</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>BR (55) CA (5,56,57) CZ (58) DK (59) ES (60–62) HU (63–65) IE (66,67) NL (68,69)</td>
<td>2–180</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>BR (1,2) CA (3,4,6–11) CZ (12–15) DE (16) DK (17–19) ES (20–29) FI (30,31) FR (32,33) HU (34–36) IE (37–40) IL (41) NL (42–48) SE (49–51) UK (52)</td>
<td>4.4–792&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>BR (55) CA (3,8,6,57) CZ (14) (18) ES (22) HU (63) IE (38,67) NL (43–47,69)</td>
<td>US (53,54)</td>
</tr>
<tr>
<td>Glycerol dibehenate</td>
<td>BR (55) CA (57) CZ (58) DK (59) ES (60–62) HU (64,65) IE (66) NL (68)</td>
<td>2.5–14</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>BR (55) CA (3,8,6,57) CZ (14) (18) ES (22) HU (63) IE (38,67) NL (43–47,69)</td>
<td>4–132</td>
</tr>
<tr>
<td>Hypermellose</td>
<td>BR (1,2,55) CA (4–8,10,56,57) CZ (12,13,15) DE (16) ES (20–23–29) FI (31) FR (32,33) HU (34,36) IE (39,40) IL (41) NL (42,48) SE (50) UK (52) US (53,54)</td>
<td>0.8–537</td>
</tr>
<tr>
<td>Lactose</td>
<td>BR (55) CA (57) CZ (58) DK (59) ES (60–62) HU (64,65) IE (66) NL (68,69)</td>
<td>23–1020&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Macrogol</td>
<td>BR (1,2,55) CA (4–11,56,57) DE (16) ES (20,23,26,27) FR (32,33) US (53,54)</td>
<td>0.12–961&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>BR (2) CA (4–11,56,57) CZ (12–14) DE (18) ES (20,22,24,26,27) FI (31) HU (63) NL (43,48,69) SE (49,51) US (53,54)</td>
<td>0.15–410&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>CA (56)</td>
<td>2.8–184</td>
</tr>
<tr>
<td>Polydextrose</td>
<td>CA (7,10)</td>
<td>3.8–8.1</td>
</tr>
<tr>
<td>Polysorbates</td>
<td>CA (4,6) US (53,54)</td>
<td>0.4–418&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poly(vinyl alcohol)</td>
<td>CA (9,11)</td>
<td>0.7–20</td>
</tr>
<tr>
<td>Povidone</td>
<td>BR (55) CA (5,57) CZ (58) DK (59) ES (60–62) HU (64,65) IE (66) NL (68,69)</td>
<td>0.8–537</td>
</tr>
<tr>
<td>Silica</td>
<td>BR (55) CA (3,9–11,56,57) CZ (12,13,58) DE (17,19,59) ES (20,21,23,24,26,27,60–62)</td>
<td>0.50–100</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>BR (55) CA (57) CZ (58) DK (59) ES (60–62) HU (63–65) IE (66,67) NL (68,69)</td>
<td>2–876&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium steryl fumarate</td>
<td>BR (1) CA (3) CZ (15) DE (16) DK (17,19) ES (21,25,28,29) FI (30) FR (32,33) HU (34–36) IE (37,39,40) IL (41) NL (42) SE (50) UK (52)</td>
<td>1.2–26</td>
</tr>
<tr>
<td>Starch</td>
<td>CA (5)</td>
<td>0.44–1135&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>CA (56) CZ (12,13) ES (20,23,24,26,27,60–62) FI (31)</td>
<td>0.9–72&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Talc</td>
<td>BR (1,55) CA (9,11,57) CZ (12,13,58) DE (16) DK (59) ES (20,23,24,26,27,60–62) FI (31) FR (32,33) HU (63–65) IE (66,67) NL (48,68,69)</td>
<td>0.10–220&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triacetin</td>
<td>CA (7,10)</td>
<td>0.72–15</td>
</tr>
</tbody>
</table>

<sup>a</sup>Colors, flavors, and ingredients present in the coating and/or the printing ink are not included.

<sup>b</sup>The approval of a drug product by the local regulatory authority. Also the terms Drug approval and registration, are used.

<sup>c</sup>Abbreviations of the countries: see, text.

<sup>d</sup>The upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.
permeability and low permeability reference standards and an apparent permeability coefficient ($P_{\text{app}}$) of levofloxacin of 28.36 ± 1.93 $10^{-6}$ cm/s was reported. In the same study, metoprolol, labetalol, and atenolol showed $P_{\text{app}}$ values of 29.88 ± 3.17 $10^{-6}$ cm/s, 18.05 ± 1.90 $10^{-6}$ cm/s, and 1.86 ± 0.47 $10^{-6}$ cm/s, respectively; hence, levofloxacin was classified as highly permeable. The authors also concluded that levofloxacin is an efflux protein substrate, although its efflux ratio was only 4:1.52 According to the Biopharmaceutical Drug Disposition Classification System (BDDCS), extensive metabolism of an API indicates a high permeability.53,54 Levofloxacin is mainly eliminated by renal excretion of the unaltered drug, hence not extensively metabolised.8,19,55–57 suggesting levofloxacin not to be highly permeable.53,54 However, BDDCS was developed as a surrogate system for situations in which no BA data are available, which is not so for levofloxacin. Moreover, discrepancies between BCS and BDDCS have been observed.58,59,60–62

Distribution, Metabolism, and Elimination

Levofloxacin is widely distributed throughout the body, with a mean volume of distribution of 1.1 L/kg and penetrates well into most body tissues and fluids. It is approximately 24%–38% bound to serum plasma proteins (primarily albumin).8,19 The drug undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. The only metabolites identified in humans are the desmethyl and N-oxide inactive metabolites, which account for less than 5% of a dose.19 Following oral administration in healthy volunteers or patients with complicated urinary infections or pyelonephritis, approximately 80%–87% of an administered dose was recovered as unchanged drug in urine,8,19,55–57 whereas less than 4% of the dose was recovered in feces.19 The excretion occurs through glomerular filtration and tubular secretion. Renal clearance and total body clearance are highly correlated with creatinine clearance ($C_{\text{cr}}$), and dosage adjustments are required in patients with significant renal dysfunction.8,19 The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 h following single or multiple doses of levofloxacin given orally or intravenously.8,19

**DOSAGE FORM PERFORMANCE**

**BE Studies**

Two reports in the literature have demonstrated BE of two different generic formulation of oral levofloxacin (500 mg) marketed in Mexico and Tavanic® (500 mg).61,62 In the first report, 26 healthy volunteers ofloxacin (500 mg) marketed in Mexico and Tavanic® of two different generic formulation of oral levofloxacin. In the first report, 26 healthy volunteers were enrolled and the 90% confidence intervals (CIs) for log-transformed $C_{\text{max}}$, AUC$_{0–24}$, and AUC$_{0–\infty}$ were 94.48%–106.22%, 90.01%–116.44%, and 85.11%–114.00%, respectively. The composition of the formulation was not reported.61 In the second report, BE was assessed in 27 male healthy subjects. The CIs for log-transformed $C_{\text{max}}$, AUC$_{0–24}$, and AUC$_{0–\infty}$ were 95.57%–111.97%, 102.73%–106.36%, and 102.04%–106.75%, respectively. The composition of formulation was not reported.62 All the results meet the current BE criteria.

**Excipients**

Excipients present in IR levofloxacin tablets with a marketing authorization (MA)* in BR63, Canada (CA)64, Czech Republic (CZ)65, Germany (DE)66, Denmark (DK)67, Spain (ES)68, Finland (FI)69, France (FR)70, Hungary (HU)71, Ireland (IE)72, Israel (IL)73, the Netherlands (NL)74, Sweden (SE)75, United Kingdom (UK)76, and US77 are summarized in Table 1. In view of their MAs and national regulations, it can be inferred that the drug products listed in Table 1 successfully passed an in vivo BE study or clinical trial. Because one formulation will most probably be registered in several countries, these drug products correspond to a far lower number of formulations. Also, it cannot be taken for granted that each and every registered drug product has successfully met the current in vivo BE criteria.78 Nevertheless, it seems safe to conclude that the risk of bioinequivalence caused by an excipient effect is low for excipients present in a large number of registered drug products, when the excipient is present in amounts not exceeding its normal use in IR tablets. Table 1 shows the range of that excipients present in solid oral dosage forms with a MA in the US.79 The approval of a drug product by the local regulatory authority. Also, the terms Drug Approval and Registration are used.

**Dissolution**

A dissolution method for levofloxacin tablets is not included in present editions of the USP, European Pharmacopoeia, British Pharmacopoeia, or the International Pharmacopoeia80–83 but the dissolution methods database of the FDA contains a test for levofloxacin tablets: USP Apparatus I (basket), 100 rpm, medium—900 mL of 0.1 N HCl at 37°C.84 In the pharmacokinetic study of Frick et al.,34 the drug product showing more than 80% of the dose absorbed after 1 h was also tested by in vitro dissolution; more than 80% of the dose was dissolved in 30 min under the following conditions: basket, 100 rpm, 900 mL of 0.1 N HCl.
DISCUSSION

Solubility

According to the current regulatory guidances, an API is highly soluble if its dose/solubility ratios (D/S) is 250 mL or less at the pH range of 1.0–6.82, 4 or 1.0–7.53 at 37°C, in which “dose” is to be understood as highest dose strength2, 3 or highest single dose administered.4 Levofloxacin’s D/S at pH 1.0–7.5 are over the range from 2.5 to 25 mL, based on 750 mg of levofloxacin as the highest dosage strength and also the highest single dose administered, and thus far less than the D/S cut-off for the “high solubility” biowaiver criteria. However, these data refer to 20°C, not at 37°C.2–4 But, if levofloxacin, like most APIs, has an endothermic heat of solution, it can be assumed that it will exhibit a higher solubility at 37°C. Therefore, it seems safe to conclude that levofloxacin is highly soluble according to BCS criteria.2–4

Permeability

Because its BA is nearly complete following oral administration, levofloxacin is highly permeable according to all BCS criteria.2–4, 8, 19, 42–45, 55–57 Data from Caco-2 studies support this classification.34, 52

BCS Classification

According to all current BCS class definitions,2–4 levofloxacin can be assigned to BCS I. Frick et al.34 and the WHO40, 85, 86 reached the same classification.

Risks with Respect to Excipient and/or Manufacturing Variations

No study directly investigating the influence of excipients on the absorption of levofloxacin has been reported. Moreover, there is no report of bioinequivalence seen in the literature.

Surrogate Techniques for in vivo BE Testing

In the highly unlikely case that a test product is bioinequivalent, and that this is caused by a large difference in in vivo desintegration and/or in vivo dissolution between test product and comparator, it is most likely that comparative in vitro dissolution of the test product versus its comparator in the three biowaiver-relevant media2–4 will be able to detect the difference.

There is presently no surrogate technique for in vivo BE testing able to detect BE caused by a difference in in vivo permeability between test product and comparator, but this risk will be low if the test product contains only excipients also present in IR levofloxacin drug products approved in ICH or associated countries in the same dosage form, as listed on Table 1.

However, one of the excipients listed in Table 1, polysorbates,87 may have an effect on the in vivo permeability. Also, levofloxacin has been reported to be a substrate of uptake transporters like OATP1A246 and efflux transporters,82 and in view of these more critical permeability characteristics, more stringent criteria are recommended when polysorbates are present in the test product. In that case, the test product should be both qualitatively and quantitatively identical to its comparator in terms of polysorbate content.4

Patient’s Risks Associated with Bioinequivalence

According to the Code of Federal Regulations, an API has a narrow therapeutic index when there is less than a twofold difference in LD50 and median effective dose (ED50) values, and/or safe and effective use of the drug products requires careful dosage titration and patient monitoring.88 Because the LD50 in rats is 1500 mg/kg13 and the ED50 range in rats is 0.18–16.3 mg/kg,89 resulting in an almost 10-fold difference, and there is generally no need to monitor blood levels, levofloxacin can be considered as a wide therapeutic index drug, according to the US FDA.88 Furthermore, Health Canada published a guidance including drugs which commonly exhibit adverse effects that limit the therapeutic use to doses close to those required for the therapeutic effect (e.g., “narrow therapeutic range drugs”) or drugs for which the therapeutic use may result in dose or concentration-dependent adverse effects, which are persistent, irreversible or slowly-reversible, or life threatening (e.g., “highly toxic drugs”), and this list does not include levofloxacin.90 Further, levofloxacin is not on the list of Narrow Therapeutic Range Drugs of the Japanese Health Authorities.91 Despite the low potential of levofloxacin for acute toxicity19 and its acceptance as a wide therapeutic index drug, it is nonetheless advisable to monitor blood glucose levels in diabetic patients and monitor hepatic functions in patients 60 years old or older taking levofloxacin.19

CONCLUSION

A biowaiver for IR solid oral dosage forms containing levofloxacin is scientifically justified, provided that (a) the test product contains only excipients present in IR levofloxacin drug products approved in ICH or associated countries in the same dosage form; (b) both the test and comparator dosage form are very rapidly dissolving or rapidly dissolving with similarity of the dissolution profiles demonstrated at pH 1.2, 4.5, and 6.8; and (c) if the test product contains polysorbates, it should be both qualitatively and quantitatively identical to its comparator in terms of polysorbate content.
ACKNOWLEDGMENTS

Arthur da Silva, Camila Costa, Camila Rediguier, Cristina Serra, Diana Nunes, Jacqueline de Souza, Kelen Soares, Varley Sousa, Taina Nunes, and Valentina Porta are acknowledged for helping the construction of this monograph that is a product from the work of Brazilian Bio waiver Working Group. Kik Groot, RIVM, is acknowledged for producing Table 1.

REFERENCES


In vitro comparison of phenoxymethylpenicillin potassium, clavipride and levofloxacin. Eur J Pharm Biopharm 46(3):305–311. Solubility data were read from Fig 1.


