COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Furosemide

G.E. GRANERO,[1] M.R. LONGHI,[1] M.J. MORA,[1] H.E. JUNGINGER,[2] K.K. MIDHA,[3] V.P. SHAH,[4] S. STAVCHANSKY,[5] J.B. DRESSMAN,[6] D.M. BARENDS[7]

[1]Chemical Sciences Faculty, Pharmacy Department, National University of Córdoba, Córdoba, Argentina

[2]Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand

[3]University of Saskatchewan, Saskatoon, Saskatchewan, Canada

[4]International Pharmaceutical Federation FIP, The Hague, the Netherlands

[5]Pharmaceutical Division, College of Pharmacy, University of Texas at Austin, Austin, Texas

[6]Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt, Germany

[7]RIVM—National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Received 29 July 2009; accepted 29 October 2009

Published online 3 December 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22030

ABSTRACT: Literature and new experimental 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 furosemide are reviewed. The available data on solubility, oral absorption, and permeability are sufficiently conclusive to classify furosemide into Class IV of the Biopharmaceutics Classification System (BCS). Furosemide's therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions and reported BE/bioavailability (BA) problems are also taken into consideration. In view of the data available, it is concluded that the biowaiver procedure cannot be justified for either the registration of new multisource drug products or major postapproval changes (variations) to existing drug products.
 J Pharm Sci 99:2544–2556, 2010
Keywords: furosemide; absorption; bioequivalence; Biopharmaceutics Classification System (BCS); permeability; solubility; regulatory science

INTRODUCTION

A biowaiver monograph of furosemide based on literature data, together with additional experimental data, is presented. The risks of basing a bioequivalence (BE) assessment on *in vitro* rather than *in vivo* study results for the approval of new IR solid oral dosage forms containing furosemide ("biowaiving"), including both reformulated products and new multisource products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing furosemide as the single active pharmaceutical ingredient (API). The purpose and scope of this series of monographs have been previously discussed.[1] 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 in terms of the probability of an incorrect biowaiver decision as well as the consequences of an incorrect 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 is advisable or not. It is pointed out that these monographs do not simply apply the various regulatory documents, but also serve as a critical

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

This article reflects the scientific opinion of the authors and not the policies of regulating agencies, the International Pharmaceutical Federation (FIP) and the World Health Organization (WHO).

Correspondence to: D.M. Barends (Telephone: 31-30-2744209; Fax: 31-30-2744462; E-mail: dirk.barends@rivm.nl)

Journal of Pharmaceutical Sciences, Vol. 99, 2544–2556 (2010)

evaluation of these documents. Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),[2] acetazolamide,[3] aciclovir,[4] amitriptyline,[5] atenolol,[1] chloroquine,[6] cimetidine,[7] diclofenac,[8] doxycyline hyclate,[9] ethambutol,[10] ibuprofen,[11] isoniazid,[12] metoclopramide,[13] prednisolone,[14] prednisone,[15] pyrazinamide,[16] propranolol,[1] quinidine,[17] ranitidine,[18] rifampicin,[19] and verapamil.[1] They are also available on-line at www.fip.org/bcs.

GENERAL CHARACTERISTICS

Name

INN name: furosemide, frusemide, fursemide. Chemical name: 4-chloro-*N*-furfuryl-5-sulphamoylanthranilic acid or 5-(aminosulfonyl)-4-chloro-2[(2-furanylmethyl)amino] benzoic acid. Its structure is shown in Figure 1.

Therapeutic Indication, Therapeutic Index, and Toxicity

Furosemide is a loop diuretic that is used orally in the treatment of edematous states associated with cardiac, renal, and hepatic failure and the treatment of hypertension.[20]

The usual dosage is 40–120 mg/day. For the treatment of mild cases of edema, doses as low as 20 mg can be effective, whereas for severe cases of edema doses as high as 600 mg/day may be required.[20] For the treatment of chronic renal impairment the dose can be as high as 1.5 g/24 h. Furosemide inhibits the reabsorption of sodium and chloride in the ascending limb of the loop of Henle and also in the early distal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced.[20] Most adverse effects of furosemide occur at high doses and/or prolonged use. Serious effects are uncommon, the most common being fluid and electrolyte imbalance, including hyponatraemia, hypokalaemia, and hypochloraemic alkalosis. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, etc.[20] There is generally no need to monitor blood levels.[20]

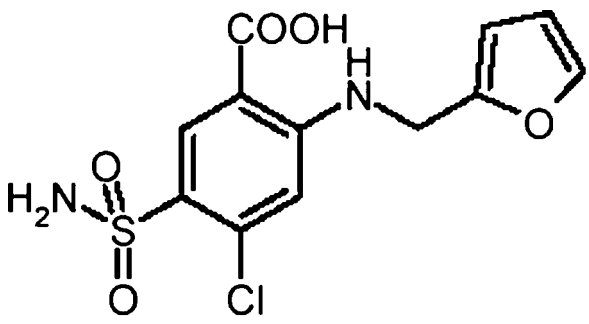

Figure 1. Structure of furosemide.

CHEMICAL PROPERTIES

Solubility

The aqueous solubility of furosemide at room temperature has been reported to be 0.01825 mg/mL.[21] Its aqueous solubility increases as function of the pH of the medium from 0.18 mg/mL at pH 2.3 to 13.36 mg/mL at pH 10.[22] Martindale reports that furosemide is practically insoluble in water, corresponding to <0.1 mg/mL.[20] The pH-solubility profile of furosemide at 30°C showed a minimum of 0.010 mg/mL at pH 2.0 and a maximum of 21.9 mg/mL at pH 8.0, followed by a marginal decrease to about 18 mg/mL above pH 8.0.[23] Other workers reported a saturation solubility at pH 4.6 and 37°C of 0.008 mg/mL.[24] The equilibrium solubility of furosemide at 37°C in Krebs Ringer buffer at pH 5.0 was 0.33 mg/mL, increasing to ~1.5 mg/mL at pH 6.5 and 1.9 mg/mL at pH 7.4.[25] New solubility data at pH values within the ranges required by the various Guidances[26–29] were measured[1] in triplicate at pH 1.0; 2.8; 3.8; 4.8; and 7.5 using the standard USP shake-flask method, with stirring for 48 h at 37°C. A summary of the literature data as well as the new data are presented in Table 1. No data on the stability of furosemide in human gastric and intestinal fluids were found in the literature.

Salts, Stereoisomers, and Polymorphs

A furosemide sodium salt is known, but is used only in parenterals, such as furosemide for injection USP.[30]

Seven polymorphic forms are known: four true polymorphs (I, II, III, IV), two solvates (IV—DMS and V—dioxane) and one amorphous form,[31–34] but polymorph-dependent bioavailability (BA) has not been reported to date in the literature.

pK_a

Furosemide is a weak acid with an acidic pK_a value of 3.8 (carboxylic acid).[35]

Partition Coefficient

Log P (*n*-octanol/water) values of 2.29[35] and 1.81[36] have been reported. Distribution coefficients at pH values of 7.39, 5.86, and 2.58 have been reported to be −1.20, −0.10, and 1.78, respectively.[36] A log D (pH 7.4) value of −0.69 has been measured.[35] Kasim et al.[37] calculated log *n*-octanol/water partition

[1]Experiments performed at the Pharmacy Department, Chemical Sciences Faculty, National University of Córdoba, Argentina. The pH was measured after the addition of the drug.

Table 1. Solubility (mg/mL) of Furosemide: Literature Data and New Experimental Data. Also shown: the Corresponding Dose/Solubility Ratio (D/S) (mL) at 37°C for three tablet strengths

			37°C		D/S Ratio[a]		
Medium, pH	25°C	30°C	Reported Data	New Experimental Data	20 mg Tablet	40 mg Tablet[b]	500 mg Tablet
Water	0.018[21]						
pH 1.0				0.014	1429[c]	2857[c]	35,714[c]
pH 1.2				0.024	833[c]	1667[c]	20,833[c]
pH 2.0		0.01[23]					
pH 2.3	0.18[22]						
pH 2.8				0.034	588[c]	1176[c]	14,705[c]
pH 3.8				0.04	500[c]	1000[c]	12,500[c]
pH 4.6			0.008[24]				
pH 4.8				0.156	128	256[c]	3205[c]
pH 5.0			0.33[25]	0.27	74	148	1852[c]
pH 6.5			1.5[25]	3.94	5.1	10	127
pH 7.4			1.9[25]				
pH 7.5				6.91	2.9	5.8	72
pH 8.0		21.9[23]		8.91	2.2	4.5	56
pH 10.0	13.36[22]						

[a]Calculated from the solubility data at 37°C; the critical limit is 250 mL.[26–29]
[b]Strength on WHO essential medicines list.[38]
[c]A D/S value exceeding the critical limit.

coefficients for furosemide using two different methods, finding values of 1.9 and 0.74, respectively. For metoprolol, following the same methodologies, the authors reported values of 1.35 and 1.72, respectively.

Oral Dosage Form Strengths

The WHO recommended oral dosage form strength is 40 mg.[38] Table 2 shows IR furosemide tablets with a marketing authorization (MA) in Germany (DE),[39] Denmark (DK),[40] Finland (FI),[41] France (FR),[42] The Netherlands (NL),[43] Norway (NO),[44] Spain (ES),[45] Sweden (SE),[46] United Kingdom (UK),[47] and the United States (US).[48] These MAs cover a very wide range of strengths: from 20 mg up to 500 mg.

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Furosemide is fairly rapidly absorbed from the gastrointestinal (GI) tract. Its BA was reported to be about 60–70%, but the absorption is variable and erratic.[20] Others report a poorer oral BA of 50%[49–51] or 37–51%.[52] Peak serum concentrations (C_{max}) occur between 60 and 90 min with concentrations falling below the limit of detection between 3 and 4 h after ingestion. The rate and extent of absorption show large inter- and intra-subject variabilities. Absorption following oral administration is influenced by the dosage form, underlying disease processes, and by the presence of food.[50] Grahnén et al.[53] investigated the intra-subject variation in BA with respect to rate and extent of absorption between two tablet formulations, Lasix® and Furix®, each in a dose of 40 mg, and also after intravenous (i.v.) administration in eight healthy subjects. Absolute BA was reported to be 56% for Lasix® and 55% for Furix®, with a range of 20–84% between individuals and 20–61% within an individual, indicating extensive variability after oral administration. Extensive variability was also observed in mean absorption time and urinary excretion. The intra-subject variability was thought to depend mainly on the absorption process, since repeated i.v. doses showed only marginal intra-subject variability, but, as this study was severely underpowered, it is not possible to draw robust conclusions from the data.

The hypothesis that furosemide exhibits site-specific absorption was investigated in the rat model. In this animal model, Chungi et al.[54] reported absorption to be biexponential and rapid when administered to the stomach but slower when administered to the small intestine. The most rapid absorption occurred after administration to the stomach at a pH of 3. In man, the absorption of furosemide is also site-specific and takes place primarily in the upper parts of the small intestine. Clear et al.[55] released furosemide using an Intelisite® capsule at specific sites in the GI tract, finding that the absorption window of furosemide in the upper GI tract is narrow: when drug release took place in the proximal intestine instead of the stomach, the area under the concentration time curve (AUC) for furosemide decreased markedly, by 29%. From these studies it was concluded that, in humans, furosemide is most rapidly absorbed from the upper GI tract following dissolution in the stomach.

Table 2. Excipients[*] present in Furosemide[†] IR solid oral drug products[‡] with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Spain (ES), Sweden (SE), United Kingdom (UK) and the United States (US)[§], and the minimal and maximal amount of that excipient present pro dosage unit in solid oral drug products with an MA in the USA[¶]

Excipient	Drug Products Containing That Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
Carmellose sodium	DE(1,2)	2.2–160
Carrageenan	DK(3) NO(4)	0.15
Cellulose	DE(1,2,5–37) DK(3,38–44) ES(45–48) FI(49–53) FR(54–56) NL(57–64) NO(4,65–69) SE(70–77) US(78–81)	4.6–1385[a]
Croscarmellose sodium	DK(40,43) FI(52) NL(57) NO(67) SE(70,74,76,77,82)	2–180
Crospovidone	DE(1,2,10,16,26,28,36) FI(49) NO(68)	4.4–792[a]
Diethyl phthalate	NL(61)	1.2–4
Ethylcellulose	NL(61)	1.0–121[a]
Gelatin	DK(83) FI(50) FR(54) NO(69)	1–756[a]
Glyceryl palmitostearate	NL(60,62,64)	18
Hydroxypropylcellulose	DE(6,7,9,11,13,15,17,18,20,22,23,25,27,29,31–33,35) NL(61)	4–132
Hypromellose	DK(3,38) NL(61) NO(4,65)	0.8–537[a]
Lactose	DE(1,2,5,6,8–21,23–37,84) DK(38–40,42–44,83,85–87) ES(45–48,88,89) FI(49,51,52) FR(55,56,90–98) NL(57-59,61,63,99–105) NO(65,67,68) SE(70,72–74,76,77,82,106,107) UK(108,109) US(78–81,110–114)	23–1020[a]
Macrogol	DE(1,2)	0.12–500[a]
Magnesium carbonate	ES(115,116)	1.1–250
Magnesium stearate	DE(1,2,5–9,11–15,17–25,27,29–35,37,84) DK(3,38–44,83,85-87) ES(45–48,88,89,115,116) FI(49–53) FR(54–56,90–98) NL(57–64,99–105) NO(4,65–69) SE(70–77,82,106,107) UK(108,109) US(81,110–114)	0.15–401[a]
Polysorbate 80	FI(49,50) NO(68,69) SE(82)	2.2–418[a]
Povidone	DE(8,10,12,16,24,26,28,34,36) DK(40,41,43) ES(115,116) FI(51–53) FR(55) NL(60,62,64,101,104,105) NO(66,67) SE(70,71,73–76,82,107) US(110)	0.17–80
Silica	DE(1,2,7,8,10,12,16,22,24,26,28,32,34,36,37,84) DK(39–41,43,86) ES(88,89) FI(50–53) FR(54–56,97) NL(58,99, 100,102,105) NO(66,67,69) SE(70,71,73–76,107) US(78–80,110,114)	0.65–99
Sodium lauryl sulphate	ES(115,116) NL(105) SE(76) US(78,79)	0.65–50
Sodium starch glycolate	DE(5–9,11–15,17–25,27,29–35,37) DK(39,42,44,85,87) ES(45–48) FI(50,51) FR(55) NL(58–60,62,64, 101,103) NO(69) SE(72,73,106) US(78,79,110,111)	2–876[a]
Starch	DE(1,2,5–7,9–11,13–23,25–33,35–37,84) DK(38–44,83,85–87) ES(45–48,88,89,115,116) FI(49,52,53) FR(54,56,90–98) NL(57–64,99–105) NO(65–68) SE(70–72,74–77,82,106,107) UK(108,109) US(78,79,81,110–114)	0.44–1135[a]
Starch, pregelatinised	DE(10,16,26,28,36,84) DK(38,85–87) ES(88,89) FI(49) FR(56,97) NL(57,61,63,99,100,102,103) NO(68) SE(77,106) UK(109) US(78,80,111–113)	6.6–600
Stearic acid	UK(108) US(78–80)	0.9–72[a]
Talc	DE(10,16,26,28,36,37,84) DK(3,38,41,83,86) ES(88,89) FI(53) FR(54,56,90–98) NL(57,58,60–62,64,99,100,104,105) NO(4,65,66) SE(71,75,77,82) US(113,114)	0.25–220[a]
Trisodium phosphate	FI(50) NO(69)	

(*Continued*)

Table 2. (*Continued*

1. Diurapid® 40 mg Tabletten (Mono). 2. Furosal® 40 mg Tabletten (Mono). 3. Diural, tabletter 250 mg og 500 mg. 4. Diural 250 mg tabletter. 5. Furosemid 40—1 A Pharma® Tabletten (Mono). 6. Furosemid 125/−500—1 A Pharma® Tabletten (Mono). 7. Furosemid 250—1 A Pharma® Tabletten (Mono). 8. Furosemid AbZ 40 mg Tabletten (Mono). 9. Furosemid AbZ 500 mg Tabletten (Mono). 10. Furosemid AL 40 Tabletten (Mono). 11. Furosemid AL 500 Tabletten (Mono). 12. Furosemid-ratiopharm® −20/−40/−125/−250 mg Tabletten (Mono). 13. Furosemid-ratiopharm® 500 mg Tabletten (Mono). 14. Furosemid Sandoz® 40 mg Tabletten (Mono). 15. Furosemid Sandoz® 500 mg Tabletten (Mono). 16. Furosemid STADA® 40 mg Tabletten (Mono). 17. Furosemid STADA® 500 mg Tabletten (Mono). 18. Diurapid® 500 mg Tabletten (Mono). 19. Furanthril® Tabletten 40 (Mono). 20. Furanthril® Tabletten 500 (Mono). 21. Furobeta® 40 mg Tabletten (Mono). 22. Furobeta® 250 mg Tabletten (Mono). 23. Furobeta® 500 mg Tabletten (Mono). 24. Furo-CT 40/−125 mg Tabletten (Mono). 25. Furo-CT 500 mg Tabletten (Mono). 26. Furogamma® 40 Tabletten (Mono). 27. Furogamma® 500 Tabletten (Mono). 28. FURO-PUREN® 40 mg Tabletten (Mono). 29. FURO-PUREN® 500 mg Tabletten (Mono). 30. Furorese® 40/−80 mg Tabletten (Mono). 31. Furorese® 125/−500 mg Tabletten (Mono). 32. Furorese® 250 mg Tabletten (Mono). 33. Furosal® 500 mg Tabletten (Mono). 34. Fusid® 40 mg Tabletten (Mono). 35. Fusid® 500 mg Tabletten (Mono). 36. Jufurix® 40 mg Tabletten (Mono). 37. Lasix® 500 mg Tabs Tabletten (Mono). 38. Diural, tabletter 20 mg og 40 mg. 39. Furese, tabletter 40 mg. 40. Furix, tabletter 20 mg og 40 mg. 41. Furix, tabletter 250 mg og 500 mg. 42. Furosemid "1A Farma," tabletter 40 mg. 43. Furosemid "DAK," tabletter 40 mg. 44. Furosemid "HEXAL," tabletter 40 mg. 45. Furosemida ANGENERICO 40 mg comprimidos EFG. 46. Furosemida BEXAL 40 mg comprimidos EFG. 47. Furosemida SANDOZ 40 mg comprimidos EFG. 48. Furosemida UR 40 mg comprimidos EFG. 49. Furesis 20/−40 mg tabletti. 50. Furesis 500 mg tabletti. 51. Furomin 40 mg tabletti. 52. Vesix® 40 mg tabletti. 53. Vesix® Special 500 mg tabletti. 54. FUROSEMIDE RATIOPHARM 40 mg cp. 55. FUROSEMIDE TEVA 40 mg cp s. 56. LASILIX SPECIAL 500mg cp s. 57. Furosemide Actavis 40 mg, tabletten. 58. Lasix 500, tabletten 500 mg. 59. Furosemide Sandoz 40 mg, tabletten. 60. Furosemide-40, tabletten 40 mg. 61. Furosemide, tabletten 40 mg (Lagap). 62. Furosemide FLX 40 mg, tabletten. 63. Furosemide ratiopharm 40 mg, tabletten. 64. Furosemide Rofold 40 mg, tabletten. 65. Diural 20 mg og 40 mg tabletter. 66. Furix tabletter 500 mg. 67. Furix tabletter 20 mg og 40 mg. 68. FUROSEMID tabletter 20 mg og 40 mg. 69. FUROSEMID tabletter 500 mg. 70. Furix 20/−40 mg tabletter. 71. Furix 500 mg tabletter. 72. Furosemid Hexal 40 mg tabletter. 73. Furosemid Nordic Drugs 40 mg tabletter. 74. Furosemid Nycomed 20/−40 mg tabletter. 75. Furosemid Nycomed 500 mg tabletter. 76. Furosemid Recip 500 mg tabletter. 77. Impugan 20/−40 mg tabletter. 78. Furosemide Tablets USP 20/−40/−80 mg. 79. Furosemide Tablets USP 20/−40/−80 mg (Roxane Laboratories). 80. Furosemide Tablets USP 20/−40/−80 mg (Mylan Pharmaceuticals, Inc.). 81. Furosemide Tablets USP 20/−40/−80 mg (Watson Labs). 82. Impugan 500 mg tablett. 83. Furosemid "DAK," tabletter 5 mg. 84. Lasix® 40 mg Tabletten (Mono). 85. Furosemid "Copyfarm," tabletter 20 mg og 40 mg. 86. Lasix, tabletter 40 mg. 87. Rosefur, tabletter 20 mg og 40 mg. 88. Furosemida KERN PHARMA 40 mg comprimidos EFG. 89. SEGURIL 40 mg comprimidos. 90. FUROSEMIDE ARROW 20/−40 mg cp s. 91. FUROSEMIDE BIOGARAN 20 mg cp/−40 mg cp s. 92. FUROSEMIDE EG 20/−40 mg cp s. 93. FUROSEMIDE MYLAN 20/−40 mg cp s. 94. FUROSEMIDE RPG 20/−40 mg cp s. 95. FUROSEMIDE SANDOZ 20/−40 mg cp s. 96. FUROSEMIDE WINTHROP 20/-40 mg cp s. 97. LASILIX 40 mg cp s. 98. LASILIX FAIBLE 20 mg cp. 99. Lasix, tabletten 40 mg. 100. Lasiletten, tabletten 20 mg. 101. Furosemide 20/−40 PCH, tabletten 20/−40 mg. 102. Furosemide 40 mg, tabletten. 103. Furosemide 20/−40 mg tabletten, tabletten. 104. Furosemide Apotex 40 mg, tabletten. 105. Furosemide CF 20/−40 mg, tabletten. 106. Furosemid Copyfarm 20/−40 mg tabletter. 107. Furosemid Recip 25/−40 mg tabletter. 108. Furosemide Tablets 20/−40/−500 mg (Actavis, UK, Ltd). 109. Furosemide Tablets BP 20/−40 mg (Wockhardt, UK, Ltd). 110. Furosemide Tablets USP 20/−40 mg (IVAX Pharmaceuticals, Inc.). 111. Furosemide Tablets USP 20/−40/−80 mg (Ranbaxy Pharmaceuticals, Inc.). 112. Furosemide Tablets USP 20/−40/−80 mg (Sandoz, Inc.). 113. Furosemide Tablets USP 20/−40/−80 mg (Qualitest Pharmaceuticals). 114. Lasix (furosemide) tablet (sanofi-aventis U.S. LLC). 115. Furosemida aphar® 40 mg comprimidos EFG. 116. Furosemida cinfa® 40 mg comprimidos EFG.

[*]Glycerol-(mono,di,tri)alkanoate, present in drug products 10, 16, 26, 28, and 36, as well as colorants and water are not included.

[†]Only single API drug products are included.

[‡]Oral solutions were excluded.

[§]Sources of data: see Oral Dosage Form Strengths Section.

[¶]USA: FDA's inactive ingredient database, http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose (version date 09-04-2009).

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

DOI 10.1002/jps

Absorptive behavior differences were reported between dosage forms. Hammarlund et al.[51] studied in 8 subjects the mean time for the different steps in absorption for i.v. and different modes oral administration of furosemide. The mean absorption times for all oral doses were significantly longer than the mean absorption times after i.v. administration, indicating absorption rate-limited kinetics. Absorptive behavior differences were also reported between solutions versus tablets. Waller et al.[56]studied two furosemide tablets and an aqueous solution in 21 healthy adult males. The peak plasma furosemide concentration obtained with the solution was significantly greater than with the tablet formulations. Also, the time to peak occurred significantly earlier with the solution. This finding was confirmed by McNamara et al.[57] evaluating the relative BA of five tablets and an oral solution in 12 normal volunteers in a crossover design; compared to the solution, all tablets formulations exhibited lower peak furosemide concentration. Absorptive behavior differences were also reported between the fasting and nonfasting state. In the study of Hammarlund et al.,[51] food delayed the absorption on average by 60 min. When a 40 or 80 mg tablet of furosemide was taken orally by healthy adults in the fasting state, a detectable concentration of drug appears in the serum within 10 min and peaks between 60 and 90 min at a level of 1–3 μg/mL,[58,59] but when taken in close proximity to a meal, there is a delay in its appearance in plasma, and a lower peak concentration of about 1 μg/mL was reported after ~2 h.[60] Despite the difference in peak serum concentrations the total amount of furosemide absorbed is similar.[60] Kelly et al.[52] also found that postprandial administration of furosemide results in delayed appearance of the drug in serum, lowered C_{max} and more prolonged concentrations. Beermann and Midskov[60] reported a reduced but parallel plasma concentration versus time profile between the fasting and postprandial states.

The pharmacokinetics of furosemide are reported to be linear over the oral dosage range of 20–80 mg.[61]

Furosemide plasma profiles often exhibit secondary or multiple peaks following either oral or i.v. administration.[52,62,63] These phenomena have been attributed to enterohepatic cycling of the drug.[50] However, furosemide is mainly excreted in the urine, largely unchanged. There is some excretion via the bile and nonrenal elimination, but the small amount of furosemide reabsorbed after biliary elimination is not sufficient to account for the secondary peaks.[20] Other authors explain the multiple plasma peaks with an erratic absorption behavior.[64] However, this hypothesis is not consistent with multiple peaks after i.v. administration.

Permeability

Several authors report permeability data of furosemide; [25,65–72] they are shown in Table 3. Furosemide is a known substrate of efflux transporters.[65] Motz[25] applied a proton gradient between an apical to basolateral compartment (A-B) transport study with A = pH 6.5 and B = pH 7.4, respectively, resulting in a flux–efflux high ratio of ~50. The large directional differences in transport rates in the Caco-2 cells have been attributed to the secretion of this API by efflux systems such as the P-glycoproteins on the one hand and to a significant paracellular contribution to passive uptake on the other hand.[68,69]

It has been reported that apparent permeability (P_{app}) of furosemide can be affected by the presence of the excipient Tween-80® (polysorbate 80). Rege et al.[70] reported an increase in the apical-to-basolateral (A-B) transport of furosemide in the presence of Tween-80®, which neutralized the asymmetry in transport. Polysorbate 80 is a known P-glycoprotein inhibitor.[73] Motz[25] confirmed the Tween-80® effect, observing not only an increase in P_{app} (A-B) but also a decrease in P_{app} basolateral-to-apical (B-A) in a Caco-2 cell model. Motz[25] also found that vitamin

Table 3. Permeability of Furosemide

Method	Furosemide ($P_{app}/P_{eff} \times 10^{-6}$ cm/s)	Metoprolol ($P_{app}/P_{eff} \times 10^{-6}$ cm/s)	Refs.
Intestinal perfusion	5.0	1300	72
Caco-2	0.11	—	65
Caco-2	0.12	23.7	66
Caco-2	0.2	23.6	67
Caco-2	0.2	—	68
Caco-2 (A-B)[a]	0.12	—	69
(B-A)[b]	2.74		
Caco-2 (A-B)	0.2	—	24
(B-A)	10.4		
Caco-2 (A-B)	0.5	—	70
(B-A)	6.46		
Caco-2 (A-B)	0.3	18.8	71

When metoprolol was included as a reference, its permeability is also reported.
[a]Apical-to-basolateral transport.
[b]Basolateral-to-apical transport.

E d-alpha-tocopheryl poly(ethylene glycol)succinate, another P-glycoprotein inhibitor,[73] increased P_{app} (A-B) of furosemide, while P_{app}(B-A) was reduced.

Distribution, Metabolism, and Elimination

Furosemide is up to 99% bound to plasma proteins.[30] The clearance of furosemide is generally reported to be in the range of 0.09–0.18 L/h/kg. The half-life of furosemide is in the range of 30–120 min and it is mainly excreted in the urine, largely unchanged.[20] In end-stage renal disease the half-life may reach almost 10 h and in neonates the half-life is also prolonged, since renal function is not yet mature at birth. As well as renal elimination there is also some excretion via the bile, with the role of nonrenal elimination considerably greater in renal impairment.[50]

Furosemide has two metabolites, furosemide glucuronide, and saluamine.

DOSAGE FORM PERFORMANCE

Excipients and/or Manufacturing Variations

Reports of BE studies between furosemide IR drug products show inconsistent results.[74–78] However, most of these studies were carried out 20–30 years ago, when BE was not defined according to the current biostatistical standards. Nowadays drug products are considered bioequivalent if, with high probability, the hypothesis that two formulations are bio*in*equivalent can be rejected,[26–29] whereas at the time most of the literature studies were conducted, two formulations were considered bioequivalent if no significant differences in pharmacokinetic parameters were observed. As a result, in several early studies formulations were reported to be bioequivalent, even though by current biostatistical standards these formulations would not have met BE criteria due to insufficient power in the study design. Additionally, most references do not report results in sufficient detail to allow recalculation of the data according to current biostatistical criteria.

Beermann et al.[74] compared the BA of two marketed brands of furosemide, Impugan® (A/S Dumex, Copenhagen, DK) and Lasix® (Hoechst AG, Frankfurt (M), DE), in five healthy volunteers. The compositions of the products were not reported. Although time of the peak levels, AUC and the urinary recovery after the oral administration did not differ significantly using Student's paired *t*-test, the power of the study was undoubtedly too weak to conclude that the two products were bioequivalent.

A Thai study[79] compared the *in vitro* dissolution and clinical response among marketed furosemide drug products. The compositions of the products were not reported. The *in vitro* dissolution of thirteen different brands of 40 mg furosemide tablets available in Thailand was evaluated. Only four brands passed the specification for dissolution (apparatus 2 at 50 rpm in pH 7.4 phosphate buffer). The original brand (brand A) and the three local brands (brand B, C, and D) which showed differences in dissolution characteristics were selected for a BA study in eight healthy subjects. Plasma furosemide concentrations and urine output, and sodium, chloride, and potassium excretion were measured. The relative BA of furosemide with respect to brand A was 70% (brand B), 113% (brand C), and 95% (brand D); these differences were deemed not statistically significant different at a 95% confidence level, but certainly at least brand A would not have met the current 0.80–1.25 criterion for the AUC. As the clinical response in terms of diuresis and electrolyte excretion between the four brands was not significantly different at a 95% confidence level, the authors concluded that the formulations were clinically equivalent. Here again, the power of the study was likely too weak to appropriately detect differences.

Awad et al.[80] estimated the BE of Diusemide versus Lasix, each containing 40 mg of furosemide, in 20 healthy volunteers. The compositions of the products were not reported. No significant differences were found in AUC, C_{max}, t_{max}, cumulative urine volume, cumulative sodium and potassium excretion. Although this analysis led the authors to conclude to BE between the two products, the power of the study was undoubtedly too weak to conclude that the products were bioequivalent using today's BE standards.

Nakib et al.[81] reported BE of a brand of furosemide 40 mg tablets versus Lasix®. The compositions of the products were not reported. The study included 24 fasting, healthy, male volunteers and 90% confidence intervals of the ratios of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the two formulations were within the 80–125% range. Applying current BE standards, the two products would be declared bioequivalent.

Cuadrado et al.[82] studied two 40 mg furosemide formulations versus a reference, the identity of which not was revealed. The compositions of the products were also not reported. The study included 24 healthy volunteers; plasma furosemide concentrations, urine output and sodium, chloride, and potassium excretions were measured. $AUC_{0-\infty}$, and C_{max} and were tested for BE after ln-transformation and ratios of t_{max} were evaluated nonparametrically. Ninety percent confidence intervals for $AUC_{0-\infty}$ were 0.94–1.19; for C_{max} 0.96–1.31 and for t_{max} 0.55–1.00, respectively and BE between both formulations was concluded by the authors for all parameters except for t_{max}. The methodology used was in line with current standards, but many regulatory authorities would conclude that these formulations do not meet current BE criteria,

 DOI 10.1002/jps

since for C_{max} an acceptance criteria of 0.8–1.25 is generally applied.

Grahnén et al.[53] reported a study of two tablet formulations, Lasix® and Furix®, each at a dose of 40 mg, in eight healthy subjects. For these subjects the products were demmed nonequivalent, based on AUC: However, after extending the study to 16 subjects, the authors considered the products to be bioequivalent, based on a <6% probability that there was a >20% difference in AUC. This criterion does not correspond to current BE criteria.

Studies suggesting bio*in*equivalence[2] between furosemide tablets have also been reported. Wolf-Coporda et al.[84] evaluated two oral preparations of furosemide, a Croatian test product and the reference preparation, Lasix® (Hoechst AG), at a dose of 500 mg in 15 healthy male volunteers. The compositions of the products were not reported. The test product showed a considerably higher C_{max}; statistically significant shorter t_{max} and significantly higher AUC than the reference preparation. The relative BA of the test product was 129% and thus not equivalent to the reference according to current BE standards. These products maybe even bio*in*equivalent, in view of the large differences in the point estimates of these pharmacokinetic parameters. The brand with the highest C_{max} also showed the fastest *in vitro* dissolution but the test conditions used were not reported.

McNamara et al.[57] evaluated three brands of 40 mg furosemide tablets, one of which was Lasix®, and one oral solution in 12 volunteers. For two brands, including Lasix®, two different batches were included in the study, one of which was designated as reference. The compositions of the formulations were not reported. Plasma and cumulative urine concentrations of furosemide were measured, as well as the *in vitro* dissolution of the tablets in USP Apparatus II (paddle) at 50 rpm in acetate buffer pH 4.6 and 5.6. With respect to the usual pharmacokinetic parameters, all tablet formulations were significantly different from the reference at the 95% confidence level, with point estimate BA ranging from 70% to 91%. This study also reported a wide intra-subject variability from oral dosage forms. Applying current BE standards, it would most probably be concluded that all tested tablet formulations failed to meet the BE criteria; some of these formulations might even be declared bio*in*equivalent.

[2]Bio*in*equivalence implies that the regulatory defined confidence interval of one, or more, BE attributes (AUC, C_{max}, T_{max}) *falls fully outside* of their regulatory acceptance range, whereas failure to meet BE criteria implies that the regulatory defined confidence interval of one, or more, BE attributes *does not fully fall inside* their regulatory acceptance range.[83]

Rubinstein and Rughani[85] studied furosemide 40 mg tablets, prepared with four different binders: polyvinylpyrrolidone, starch mucilage, stearic acid, and methylhydroxyethyl cellulose. BA was assessed in four healthy males with reference to an oral solution. The tablets containing polyvinylpyrrolidone and methylhydroxyethyl cellulose showed point estimate of relative BA values of 72% and 72%, respectively, while the starch mucilage formulation and the stearic acid formulation showed relative BA values of 54% and 35%, respectively. This considerable decrease of the BA of furosemide by starch and stearic acid was not confirmed by other excipient interaction data, see below. As this study was severely underpowered, it is not possible to draw any robust conclusions from the data.

Table 2 shows the excipients present in IR furosemide tablets with an MA in various countries. As over the years the criteria for BE have been changed, it cannot be assumed that all these drug products successfully had passed an *in vivo* BE study that would be in conformity with the present regulations. However, in view of their MA, there can be little doubt on their clinically efficacy and safety. It can therefore be argued that the excipients present in these drug products do not exert a significant effect on the rate and extent of absorption of furosemide. Table 2 includes polysorbate 80, an excipient which showed an effect on the Caco-2 permeability of furosemide.[70] This suggests that the Caco-2 excipient interaction studies may have over-discriminated. Table 2 also includes starch and stearic acid, excipients which were reported by Rubinstein and Rughani to decrease the BA of furosemide considerably is possible that the amounts used were quite different between the test formulations and those described in Table 2.

Dissolution and *In Vitro–In Vivo* Correlations (IVIVCs)

The USP 32 specification for dissolution of furosemide tablets is not <80% (Q) dissolved in 60 min in 900 mL of pH 5.8 phosphate buffer, using the paddle apparatus at 50 rpm.[30]

There are some reports describing successful IVIVCs for furosemide drug products.[82–86] Rubinstein and Rughani[85] reported that the observed differences in BA of furosemide tablets with different excipients were reflected in *in vitro* drug release in distilled water. Stüber et al.[86] studied the BA of six commercial tablet preparations in six volunteers. The identities and the composition of the tested tablets were not reported. One tablet reached only 80% of the AUC of the reference tablet; its C_{max} was lower and its t_{max} longer. The tablet with the lowest BA in term of AUC, C_{max}, and t_{max} also showed lower *in vitro* dissolution than the reference tablet in each of four different methods: pH 7.8/paddle 25 rpm; pH 7.8/

paddle 50 rpm; pH 5.3/paddle 50 rpm and flow-through cell/pH 7.8. The difference *in vitro* dissolution was most pronounced at pH 5.3/paddle 50 rpm; under this condition the time needed to reach 50% dissolution for the tablet with the low BA was 4.4 times greater than the reference.

Investigating the dissolution of two brands of furosemide tablets Prasad et al.[87] found negligible differences at pHs higher than 4.6; the brand dissolving poorly at pH 4.6 also had an inferior BA with respect to both C_{max} and AUC. In a study of four commercial and two experimental furosemide tablets Kingsford et al.[88] reported a good correlation between the percentage dissolved in 30 min in buffer pH 5.0 at 37°C in the rotating basket and the percentage of furosemide recovered in the urine.

McNamara et al.[57] tested five lots of furosemide tablets for dissolution in acetate buffer at pH values of 4.6 and 5.6, using a USP paddle apparatus at 50 rpm at pH 4.6 and 5.6. The products dissolved faster and more completely at pH 5.6. Correlations of mean *in vivo* parameters with *in vitro* dissolution approached statistical significance, with a somewhat higher correlation with the parameters derived from dissolution at pH 4.6 than at pH 5.6. However, since two products showing only small differences in pharmacokinetic parameters exhibited marked differences in dissolution at pH 4.6, the authors concluded that this medium was overly discriminating and that the pH 5.6 medium would be more appropriate for assuring batch uniformity and BE of furosemide products.

Waller et al.[56] compared tablets *in vivo* and *in vitro* of identical composition but produced by a slightly different manufacturing method. The *in vivo* study in 21 healthy human volunteers showed the relative BAs of two tablets to be 89% and 101% compared to the solution, respectively, as determined by AUC, and these were reported to be not different at a 95% confidence level. After 30 min dissolution testing at pH 5.8 in the paddle apparatus operated at 50 rpm, one tablet showed 83% dissolution, the other tablet 49% dissolution. Under the same conditions, but using a medium composed at pH 4.6, the same tablets released 41% and 17%, respectively. Since the two products show only small differences in pharmacokinetic parameters, but marked differences in dissolution at pH 5.8, and even larger differences at pH 4.6, this study suggested that dissolution testing of furosemide tablets tends to be overly discriminating, particularly at pH 4.6. Qureshi and McGilveray[89] reported a collaborative study on the *in vitro* dissolution of 40-mg furosemide tablets in buffer pH 5.8 and buffer at pH 4.6. About 20–38% of the variability in dissolution was not product related but came from the dissolution test itself.

DISCUSSION

Solubility

Solubility criteria defined in present regulatory guidances[26–29] for classifying an API as *highly soluble* require the highest dosage strength to be soluble at 37°C in 250 mL aqueous solution over the pH range of 1.0–6.8, according to the EU[28,29] and WHO[26] guidances, or 1.0–7.5 according to the FDA guidance.[27] The dose to solubility ratio (D/S) at 37°C of the most often used strength, 40 mg, exceeds the critical value of 250 mL at pH 4.8 and below; the 500 mg tablet exceeds the critical D/S value at pH 5.0 and below, see Table 1. Hence, furosemide is not *highly soluble*.

Absorption and Permeability

The FDA defines *highly permeable* as having a fraction dose absorbed of not <90%.[27] The WHO Guideline set a limit of not <85% of the fraction dose absorbed.[90] The EMEA Note for Guidance presently in force is less precise, stating that "linear and complete absorption indicating high permeability reduces the possibility of an IR dosage form influencing the BA."[28] The draft revision to that Guidance states that an extent of absorption ≥85% is generally related to high permeability.[29]

Furosemide is incompletely absorbed after oral administration to healthy subjects and also in patients with various diseases.[59,91] Additionally, Attachment A of the FDA Guidance classifies furosemide as having low permeability.[27]

Caco-2 data are in line with that classification. For drug transport in Caco-2 monolayers, a cutoff point for *highly permeable* APIs of $P_{app} = 10^{-5}$ cm/s, was proposed to ensure a fraction dose absorbed higher than 95%.[92] Similarly, a cutoff limit of P_{app} from 2×10^{-6} to 10^{-5} cm/s as a boundary of *highly permeable* were proposed by Rinaki et al.[93] Other workers proposed that a cutoff limit of P_{app} of 2×10^{-6} cm/s in Caco-2 is commensurate with 100% absorption.[94] The apical-to-basolateral, that is, the absorptive P_{app} values reported for furosemide, being in the range of $0.1–0.5 \times 10^{-6}$ cm/s, are a factor of 4–20 below these boundary values. It can be questioned if absolute Caco-2 permeability data are not so laboratory specific that a general limit cannot be set. However, Table 3 shows that in all studies where metoprolol was included as a reference, the permeability of furosemide was far lower than the permeability of metoprolol; metoprolol is the reference substance in classifying any other substance as *highly permeable* or *not highly permeable*. And the log P and C log P values are likewise in line with the classification of furosemide as *not highly permeable*, although correlations of log P values with human intestinal permeability show both false positives and negatives.[37]

 DOI 10.1002/jps

BCS Classification

The most recent WHO Guideline,[90] as well as Kasim et al.[37] and Lindenberg et al.,[95] all classify furosemide as Biopharmaceutics Classification System (BCS) Class IV. Moreover, Wu and Benet[96] classified furosemide as Class IV in their Biopharmaceutics Drug Disposition Classification System (BDDCS), a system using the disposition characteristics of an API as an estimate of its GI permeability. On the basis of literature data presented in this monograph, new data generated, as well as the classification of furosemide by other groups, it can be concluded that furosemide belongs to BCS Class IV.

Risk of Nonequivalence Caused by Excipients and/or Manufacturing

Many studies reported in the literature asserted that the drug products studied were bioequivalent, but most studies used small subject numbers and statistical methods that do not meet current requirements. Only the Nakib et al.[81] and Cuadrado et al.[82] studies appeared to have reached a BE conclusion based on currently accepted methodology. On the other hand, in the Thai,[79] Wolf-Coporda et al.,[84] McNamara et al.,[57] and Rubinstein and Rughani[85] studies, at least one of the products showed such large differences in pharmacokinetic parameters from those of the comparator that it is most likely that that product would be declared bio*in*equivalent after application of statistical testing. Although most of these products were exploratory or test formulations, the results indicate that changes in composition and/or variations in manufacturing techniques can indeed have an impact on the BA of furosemide.

Surrogate Techniques for *In Vivo* BE Testing

A variety of dissolution test conditions have been used to link *in vitro* to *in vivo* performance. In general, the results indicate that dissolution in media with a pH in the range of pH 5.0 to 5.8, that is, the pH of the USP dissolution test, will detect differences in BA. Testing in more acidic dissolution media, such as pH 4.6, tends to be overly discriminating, whereas tests in more alkaline media, such as pH 7.8, tend to lose discrimatory power. To date, however, there are not enough data with any one set of *in vitro* test conditions to allow a firm conclusion on its reliability as a predictor for *in vivo* performance.

Further, there are hints in the literature data that *in vitro* permeability of furosemide may show an excipient interaction and there is not enough evidence to rule out the possibility of such an interaction *in vivo*. It is noted that *in vitro* dissolution testing is not indicative for *in vivo* permeability effects.

Patient's Risks Associated With Nonequivalence

The regulations of the FDA, the WHO, and also the draft Guideline on BE of the EU exclude Narrow Therapeutic Index (NTI) drugs from biowaiving.[26,27,29] The therapeutic plasma concentration for furosemide ranges from 1 to 6 μg/mL, with toxicity occurring in the range 25–30 μg/mL.[97] According to the FDA definition of NTI,[98] furosemide is not a NTI drug, since there is more than a twofold difference between the minimum toxic concentration (25 μg/mL) and the minimum effective plasma concentration (1 μg/mL). The Pan American Health Organization PAHO classified furosemide as an intermediate health-risk drug in view of the margin between the nontoxic maximum and effective minimum concentrations and its adverse effects. This organization classified furosemide as having an intermediate probability of a minor complication of the disease and/or mild adverse reactions at plasma concentrations outside the therapeutic window of the drug.[99] The current EU regulation does not mention the concept of NTI, but states that noncritical therapeutic range should be considered, defined as requirements of special precautions with respect to precision and accuracy of dosing, for example, the need for critical plasma concentrations.[28]

Furosemide is used for serious indications such as cardiac insufficiency and pulmonary hypertension. In many therapeutic situations, including edema of varying severity and oliguria, dose titration in the individual patient is recommended.[20] This is partly because furosemide shows large intra- and inter-subject variabilities in BA after oral administration and partly due to variability in patient response to furosemide. Although a bio*in*equivalence between two furosemide drug products could easily bemasked by the large intra- and inter-subject variabilities in BA and the dose titration, approving drug products which cannot meet BE criteria is not an option for health authorities.

CONCLUSION

Furosemide is BCS Class IV, so both the *in vivo* dissolution and the *in vivo* permeability can be critical to *in vivo* performance of oral furosemide drug products. No data are available in the literature about its stability in human gastric and intestinal fluids. Likewise, no surrogate methods have been identified in the literature that would reliably forecast the *in vivo* performance of oral furosemide products. Further, *in vivo* excipient effects on permeability of furosemide cannot fully be ruled out. Therefore, a biowaiver for the approval of new multisource IR solid oral products containing furosemide is inappropriate and BE should be

established with an *in vivo* BE study. This conclusion supports current regulatory guidances[26–29] which do not allow biowaivers for new multisource drug products containing BCS Class IV APIs.

Changes in approved drug products, such a change in the manufacturing formula, in the manufacturing process, in manufacturing sites and/or equipment also necessitate demonstration of BE. If small, such changes may be approvable without an *in vivo* BE study. The FDA describes such postapproval changes as SUPAC level 1 and level 2.[100] The EU has a comparable system.[101] When a change to an approved furosemide IR drug product falls into such category, the data presented in this monograph (including the excipient table for products with an MA) can be helpful to assess how critical the change is to product BE.

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. Kalantzi 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: Acetaminophen (Paracetamol). J Pharm Sci 95:4–14.
3. Granero GE, Longhi MR, Becker C, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Acetazolamide. J Pharm Sci 97:3691–3699.
4. Arnal J, Gonzalez-Alvarez I, Bermejo M, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Aciclovir. J Pharm Sci 97:5061–5073.
5. Manzo RH, Olivera ME, Amidon GL, Shah VP, Dressman JB, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms: Amitriptyline Hydrochloride. J Pharm Sci 95:966–973.
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. 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.
8. Chuasuwan B, Binjesoh V, Polli JE, Zhang H, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2009. Biowaiver monographs for immediate release solid oral dosage forms: Diclofenac sodium and diclofenac potassium. J Pharm Sci 98:1206–1219.
9. Jantratid E, Strauch S, Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2009. Biowaiver monographs for immediate release solid oral dosage forms: Doxycycline hyclate. J Pharm Sci Epub ahead of print.
10. Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Ethambutol dihydrochloride. J Pharm Sci 97:1350–1360.
11. 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.
12. Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Isoniazid. J Pharm Sci 96:522–531.
13. Stosik AG, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Metoclopramide hydrochloride. J Pharm Sci 97:3700–3708.
14. Vogt M, Derendorf H, Krämer 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.
15. Vogt M, Derendorf H, Krämer 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.
16. Becker C, Dressman JB, Junginger HE, Kopp S, Shah VP, Stavchansky S, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Pyrazinamide. J Pharm Sci 97:3709–3720.
17. Grube S, Langguth P, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2009. Biowaiver monographs for immediate release solid oral dosage forms: Quinidine sulfate. J Pharm Sci 98:2238–2251.
18. Kortejärvi H, Yliperttula M, Dressman JB, Junginger HE, Midha KK, Shah VP, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms: Ranitidine hydrochloride. J Pharm Sci 94:1617–1625.
19. Becker C, Dressman JB, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2009. Biowaiver monographs for immediate release solid oral dosage forms: Rifampicine. J Pharm Sci 98:2252–2267.
20. Sweetman S, editor. 2009. Martindale: The complete drug reference. Electronic version. Pharmaceutical Press, Thomson/MICROMEDEX, London, UK/Greenwood Village, Colorado.
21. Shin S-C, Kim J. 2003. Physicochemical characterization of solid dispersion of furosemide with TPGS. Int J Pharm 251:79–84.
22. Rowbotham PC, Stanford JB, Sugden JK. 1976. Some aspects of the photochemical degradation of frusemide. Pharm Acta Helv 51:304–307.
23. Devarakonda B, Otto DP, Judefeind A, Hill RA, de Villiers M. 2007. Effect of pH on the solubility and release of furosemide from polyamidoamine (PAMAM) dendrimer complexes. Int J Pharm 345:142–153.
24. Maestrelli F, Garcia-Fuentes M, Mura P, Alonso MJ. 2006. A new nanocarrier consisting of chitosan and hydroxypropylcyclodextrin. Eur J Pharm Biopharm 63:79–86.
25. Motz SA. 2007. Combined assessment of dissolution and epithelial permeability of solid oral dosage forms. Ph.D Thesis

Universität Saarland. http://deposit.ddb.de/cgi-bin/dokserv?-idn=983385645&dok_var=d1&dok_ext=pdf&filename=&filename= 983385645. pdf (accessed May 18, 2009).
26. WHO. 2006. Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability. Technical Report Series, No. 937, 40th Report, Annex 7 of WHO Expert committee on specifications for pharmaceutical preparations. http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf. (accessed May 18, 2009).
27. FDA. 2000. Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System. US Food and Drug Administration, Center for Drug Evaluation and Research, USA. http://www.fda.gov/cder/guidance/3618fnl.pdf. (accessed May 18, 2009).
28. EMEA. 2001. Note for guidance on the investigation of bioavailability and bioequivalence. http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf.
29. EMEA. 2008. Draft Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev.1. (accessed May 18, 2009). http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf.
30. The United States Pharmacopeial Convention, Inc. 2009. USP;1; 32—NF 27. The United States Pharmacopeia—The National Formulary, Rockville MD 2085.
31. Matsuda Y, Tatsumi E. 1990. Physicochemical characterization of furosemide modifications. Int J Pharm 60:11–26.
32. Beyers H, Malan SF, van der Watt JG, de Villiers MM. 2000. Structure-solubility relationship and thermal decomposition of furosemide. Drug Dev Ind Pharm 26:1077–1083.
33. Pudipeddi M, Serajuddin TM. 2005. Trends in solubility of polymorphs. J Pharm Sci 94:929–939.
34. Latosinska JN, Latosinska M, Medycki W, Osuchowicz J. 2006. Molecular dynamics of solid furosemide (4-chloro-2-furfurylamino-5-sulfamoyl-benzoic acid) studied by NMR and DFT methods. Chem Phy Lett 430:127–132.
35. Berthod A. 1999. Hydrophobicity of ionizable compounds. A theoretical study and measurements of diuretic octanol-water partition coefficients by countercurrent chromatography. Anal Chem 71:879–888.
36. Ruiz-Angel MJ, Carda-Broch SC, García-Alvarez-coque MC, Berthod A. 2004. Micellar versus hydro-organic mobile phases for retention-hydrophobicity relationship studies with ionizable diuretics and an anionic surfactant. J Chromatogr A 1030:279–288.
37. 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.
38. WHO. WHO model list of essential medicines. 16th list, March 2009. http://www.who.int/selection_medicines/committees/expert/17/WEB_unedited_16th_LIST.pdf. (accessed May 8, 2009).
39. ROTE LISTE® Arzneimittelverzeichnis für Deutschland. http://www.rote-liste.de. (accessed May 8, 2009).
40. The Danish Medicines Agency. http://www.dkma.dk. (accessed May 8, 2009).
41. National Agency for Medicines. http://www.nam.fi. (accessed May 15, 2009).
42. VIDAL. Fiches médicaments. http://www.vidal.fr. (accessed May 15, 2009).
43. College ter Beoordeling van Geneesmiddelen—Medicines Evaluation Board. http://www.cbg-meb.nl. (accessed May 8, 2009).
44. Norwegian Medicines Agency. http://www.legemiddelverket.no. (accessed May 15, 2009).
45. Agencia Española de Medicamentos y Productos Sanitarios. http://www.agemed.es. (accessed May 15, 2009).
46. Läkemedelsverket. http://www.lakemedelsverket.se. (accessed May 15, 2009).
47. Datapharm Communications Ltd. http://www.medicines.org.uk. (accessed May 15, 2009).
48. DailyMed. http://www.dailymed.nlm.nih.gov. (accessed May 15, 2009).
49. Ponto LL, Schoenwald RD. 1990. Furosemide (frusemide). A pharmacokinetic/pharmacodynamic review (Part I). Clin Pharmacokinet 18:381–408.
50. Ponto LL, Schoenwald RD. 1990. Furosemide (frusemide). A pharmacokinetic/pharmacodynamic review (Part II). Clin Pharmacokinet 18:460–471.
51. Hammarlund MM, Paalzow LK, Odlind B. 1984. Pharmacokinetics of furosemide in man after intravenous and oral administration: Application of moment analysis. Eur J Clin Pharmacol 26:197–207.
52. Kelly MR, Cutler RE, Forrey AW, Kimpel BM. 1973. Pharmacokinetics of orally administered furosemide. Clin Pharmacol Ther 15:178–186.
53. Grahnén A, Hammarlund M, Lundqvist T. 1984. Implications of intraindividual variability in bioavailability studies of furosemide. Eur J Clin Pharmacol 27:595–602.
54. Chungi VS, Dittert LW, Smith RB. 1979. Gastrointestinal sites of furosemide absorption in rats. Int J Pharm 4:27–38.
55. Clear NJ, Milton A, Humphrey M, Henry BT, Wulff M, Nichols DJ, Anziano RJ, Wilding I. 2001. Evaluation of the intelisite capsule to deliver theophylline and frusemide tablets to the small intestine and colon. Eur J Pharm Sci 13:375–384.
56. Waller ES, Crismon M, Smith R, Bauga M, Doluisio J. 1988. Comparative bioavailability of furosemide from solution and 40 mg tablets with different dissolution characteristics following oral administration in normal men. Biopharm Drug Dis 9:211–218.
57. McNamara PJ, Foster TS, Digenis GA, Patel RB, Craig WA, Welling PG, Rapaka RS, Prasad VK, Shah VP. 1987. Influence of tablet dissolution of furosemide bioavailability: A bioequivalence study. Pharm Res 4:150–153.
58. Kelly MR, Cutler RE, Forrey AW, Kimpel BM. 1973. Pharmacokinetics of orally administered furosemide. Clin Pharmacol Ther 15:178–186.
59. Cutler RE, Blair AD. 1979. Clinical pharmacokinetics of frusemide. Clin Pharmacokinet 4:279–296.
60. Beermann B, Midskov C. 1986. Reduced bioavailability and effect of furosemide given with foof. Eur J Clin Pharmacol 29:725–727.
61. Waller ES, Massarella JW, Tomkiw MS, Smith RV, Doluisio JT. 1985. Pharmacokinetics of furosemide after three different single oral doses. Biopharm Drug Dispos 6:109–117.
62. Smith DE, Lin ET, Benet LZ. 1980. Absorption and disposition of furosemide in healthy volunteers, measured with a metabolite-specific assay. Drug Metab Dis 8:337–342.
63. Waller E, Hamilton SF, Massarella JW, Sharanevych MA, Smith RV, Yakatan GJ, Doluisio JT. 1982. Disposition and absolute bioavailability of furosemide in healthy males. J Pharm Sci 71:1105–1108.
64. Lennernas H, Knutson L, Knutson T, Lesko L, Salmonson T, Amidon GL. 1995. Human effective permeability data for furosemide, hydrochlothiazide, ketoprofen and naproxen to be used in the proposed biopharmaceutical classification for IR products. Pharm Res 12:S-396.
65. Yamashita S, Furubayashi T, Kataoka M, Sakane T, Sezaki H, Tokuda H. 2000. Optimized conditions for prediction of intestinal drug permeability using Caco-2 cells. Eur J Pharm Sci 10:195–204.
66. Corti G, Maestrelli F, Cirri M, Zerrouk N, Mura P. 2006. Development and evaluation of an in vitro method for

prediction of human drug absorption II. Demonstration on the method suitability. Eur J Pharm Sci 27:354–362.
67. Jung SJ, Choi SO, Um SY, Il Kim JI, Choo HYP, Cho SYi, Chung SY. 2006. Prediction of the permeability of drugs through study on quantitative structure-permeability relationship. J Pharm Biom Anal 41:469–475.
68. Flanagan SD, Benet LZ. 1999. Net secretion of furosemide is subject to indomethacin inhibition, as observed in Caco-2 monolayers and excised rat Jejunum. Pharm Res 16:221–224.
69. Pade V, Stavchansky S. 1997. Estimation of the relative contribution of the transcellular and paracellular pathway to the transport of passively absorbed drugs in Caco-2 cell culture model. Pharm Res 14:1210–1215.
70. 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.
71. Hilgendorf C, Spahn-Langguth H, Regardh CG, Lipka E, Amidon GL, Langguth P. 2000. Caco-2 versus Caco-2/HT29-MTX co-cultured cell lines: Permeabilities via diffusion, inside- and outside directed carrier-mediated transport. J Pharm Sci 89:63–75.
72. Winiwarter S, Bonham NM, Ax F, Hallberg A, Lennernäs H, Karlén A. 1998. Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. J Med Chem 41:4939–4949.
73. Collnot EM, Baldes C, Wempe MF, Hyatt J, Navarro L, Edgar KJ, Friedrich Schaeffer U, Lehr CM. 2006. Influence of vitamin ETPGS poly(ethylene glycol) chain length on apical efflux transporters in Caco-2 cell monolayers. J Control Release 111:35–40.
74. Beermann B, Dalen E, Lindstrom B. 1978. Bioavailability of two furosemide preparations. Br J Clin Pharmacol 6:537–538.
75. Eggers NJ, Kingsford M, Saint Joly CM, Jellett LB, Maling TJ. 1980. Bioavailability of furosemide. N Z Med J 91:403–404.
76. Habermann W, Rudolph F. 1980. Bioequivalence studies with furosemide. N Z Med J 92:476.
77. Martin BK, Uihlein M, Ings RM, Stevens LA, McEwen J. 1984. Comparative bioavailability of two furosemide formulations in humans. J Pharm Sci 73:437–441.
78. Straughn AB, Wood GC, Raghow G, Meyer MC. 1986. Bioavailability of seven furosemide tablets in man. Biopharm Drug Dis 7:113–120.
79. Kaojarern S, Poobrasert O, Utiswannakul A, Kositchaiwat U. 1990. Bioavailability and pharmacokinetics of furosemide marketed in Thailand. J Med Assoc Thai 73:191–197.
80. Awad R, Arafat T, Saket M, Saleh M, Gharaibeh M, Zmeili S, Sallam E, Shubair M, Qobrosi S. 1992. A bioequivalence study of two products of furosemide tablets. Int J Clin Pharmacol Ther Toxicol 30:18–23.
81. Nakib N, Idkaidek N, Beshtawi M, Bader M, Admour I, Alam SM, Zaman Q, Dham R. 2003. Bioequivalence evaluation of two brands of furosemide 40 mg tablets (Salurin and Lasix) in healthy human volunteers. Biopharm Drug Dis 24:245–249.
82. Cuadrado A, Rodríguez Gascón A, Hernández RM, Castilla AM, de la Maza A, Yánez C, López de Ocáriz A, Solinís MA, Pedraz JL. 2003. In vivo pharmacokinetic-pharmacodynamic relationship and in vitro equivalence of two oral furosemide tablet formulations. Arzneimittelforschung Drug Res 53:321–329.
83. Yu LX. 2004. BioINequivalence: Concept and Definition. ACPS Meeting, October 19–20. http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4078 S2_07_YU.ppt. (accessed October 25, 2009).
84. Wolf-Coporda A, Lovrić Z, Huić M, Francetić I, Vrhovac B, Plavsić F, Skreblin M. 1996. Determination of bioequivalence of two furosemide preparations; the effect of high doses of furosemide on some pharmacokinetic parameters. Int J Clin Pharmacol Res 16:83–88.
85. Rubinstein MH, Rughani JM. 1978. The effect of four tablet binders on the bioavailability of frusemide from 40MG tablets. Drug Dev Ind Pharm 4:541–553.
86. Stüber W, Mutschler E, Steinbach D. 1982. The pharmaceutical and biological availability of commercial preparations of furosemide. Arzneimittelforschung Drug Res 32:693–697.
87. Prasad VK, Rapaka RS, Knight PW, Cabana BE. 1982. Dissolution medium—A critical parameter to identify bioavailability problems of furosemide tablets. Int J Pharm 11:81–90.
88. Kingsford M, Eggers NJ, Soteros G. 1984. An in vivo–in vitro correlation for the bioavailability of frusemide tablets. J Pharm Pharmacol 36:536–538.
89. Qureshi SA, McGilveray IJ. 1998. Assessment of pharmaceutical quality of furosemide tablets from multinational markets. Drug Dev Ind Pharm 24:995–1005.
90. WHO. 2006. 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 of WHO Expert committee on specifications for pharmaceutical preparations. http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf. (accessed July 22, 2009).
91. Hammarlund-Idemaes M, Benet LZ. 1989. Furosemide pharmacokinetics and pharmacodynamics in health and disease—An update. J Biopharmacokinet Biopharm 17:1–46.
92. Artursson P, Palm K, Luthaman K. 2001. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Adv Drug Del Rev 46:27–43.
93. Rinaki E, Valsami G, Macheras P. 2003. Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio. Pharm Res 20:1917–1925.
94. 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.
95. 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.
96. 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.
97. Schulz M, Schmoldt A. 2003. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 58:447–474.
98. FDA. Code of Federal Regulations. Title 21, Part 320: Bioavailability and Bioequivalence requirements. Section 320.33. 2003. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.33. (accessed May 18, 2009).
99. PAHO. Science based criteria for bioequivalence in vivo and in vitro, biowaivers, and strategic framework for implementation. http://www.paho.org/english/ad/ths/ev/be-doct-draft-eng.pdf. (accessed May 18, 2009).
100. 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.
101. 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.