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DAPSONE (DAPSONUM)

Draft proposal for revision in *The International Pharmacopoeia*

(16 December 2025)

DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to **Ms Sinéad Jones** (jonessi@who.int, nsp@who.int).

Comments should be submitted through the online platform on or by **16 February 2026**. Please note that only comments received by this deadline will be considered for the preparation of this document.

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37 SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/23.919

38 **DAPSONE (DAPSONUM)**

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Description	Date
Drafting of the monograph based on information found in the public domain and other pharmacopoeias.	January 2023
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications.	April 2023
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications	May 2024
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications	April 2025
Discussion at the 59 th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	October 2025
Public consultation	December 2025 – February 2026
Further follow-up action as required.	

40

41 *[Note from the Secretariat. It is intended to revise the monograph on Dapsone. The*
42 *revision is based on information found in the public domain and in other*
43 *pharmacopoeias and submitted by a manufacturer.*

44 *Changes are indicated by insert or replace.*]

45

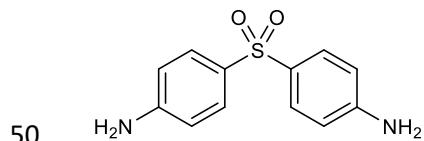
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DAPSONE (DAPSONUM)

47 **Molecular formula.** C₁₂H₁₂N₂O₂S

48 **Relative molecular mass.** 248.3

49 **Graphic formula.**



51 **Chemical name.** 4,4'-Sulfonyldianiline; 4,4'-sulfonylbis[benzenamine]; 4,4'-
52 diaminodiphenylsulfone; CAS Reg. No. 80-08-0.

53 **Description.** A white or slightly yellowish-white creamy white, crystalline powder;
54 odourless.

55 **Solubility.** Practically insoluble in water R, freely soluble in acetone R, sparingly
56 soluble in ethanol (~750 g/L) TS. It dissolves in dilute mineral acids Soluble in 7000
57 parts of water and in 30 parts of ethanol (~750 g/l) TS; soluble in acetone R.

58 **Category.** Antileprotic.

59 **Storage.** Dapsone should be kept in a tightly closed container, protected from light.

60 **Additional information.** Even in the absence of light, Dapsone is gradually degraded
61 on exposure to a humid atmosphere, the decomposition being faster at higher
62 temperatures. Dapsone shows polymorphism.

63 **Requirements**

64 **Definition.** Dapsone contains not less than 99.0% and not more than 101.0% of
65 C₁₂H₁₂N₂O₂S, calculated with reference to the dried substance.

66 **Identity tests**

67 • Either test A alone, or any two of tests B, C, D and E, may be applied.

68 A. Carry out the test as described under 1.7 Spectrophotometry in the infrared
69 region. The infrared absorption spectrum is concordant with the spectrum
70 obtained from dapson RS or with the reference spectrum of dapson.

71 If the spectra thus obtained are not concordant, repeat the test using the
72 residues obtained by separately dissolving the test substance and dapson RS in
73 a small amount of acetone R and evaporating to dryness. The infrared
74 absorption spectrum is concordant with the spectrum obtained from dapson
75 RS.

76 B. The absorption spectrum of a 5.0 µg/mL solution in methanol R, when
77 observed between 230 nm and 350 nm, exhibits maxima at about 260 nm and
78 295 nm; the absorbances of a 1-cm layer at the maximum wavelength of 260
79 nm and 295 nm are about 0.36 and 0.60, respectively.

80 Alternatively, in combination with identity test C, where a diode array detector
81 is available, record the UV spectra of the principal peaks in the chromatograms
82 with a diode array detector in the range of 230 nm to 350 nm. The UV
83 spectrum of the principal peak in the chromatogram obtained with solution (1)
84 corresponds to the UV spectrum of the peak due to dapson in the
85 chromatogram obtained with solution (2).

86 C. Carry out the test as described under 1.14.1, Chromatography, High-
87 performance liquid chromatography using the conditions and solution (1) given
88 under Related substances. For solution (2), prepare a solution containing 0.4
89 mg of dapson RS per mL of a mixture of 50 volumes of water R and 50
90 volumes of acetonitrile R. The retention time of the principal peak obtained

91 with solution (1) corresponds to the retention time of the peak due to dapsone
92 in the chromatogram obtained with solution (3)

93 D. Carry out the test as described under 1.14.1 Chromatography, Thin-layer
94 chromatography, using silica gel R6as the coating substance and a freshly
95 prepared mixture of dichloromethane R, methanol R and ammonia (~260 g/L)
96 TS (90:10:2 V/V/V) as the mobile phase. Apply separately to the plate, 5 µL of
97 each of the following 2 solutions in methanol R containing (A) 1 mg of the test
98 substance per mL, and (B) 1 mg of dapsone RS per mL. Develop the plate.
99 After removing the plate from the chromatographic chamber, allow it to dry in
100 air or in a current of air. Examine the chromatogram under ultraviolet light
101 (254 nm and 365 nm). The principal spot in the chromatogram obtained with
102 solution (A) corresponds in position, appearance and intensity with the spot due
103 to dapsone in the chromatogram obtained with solution (B). A. The
104 absorption spectrum of a 5.0 µg/mL solution in methanol R, when observed
105 between 230 nm and 350 nm, exhibits maxima at about 260 nm and 295 nm;
106 the absorbances of a 1-cm layer at the maximum wavelength of 260 nm and
107 295 nm are about 0.72 and 1.20, respectively.

108 B. See the test described below under "Related substances". The principal spot
109 obtained with solution A corresponds in position, appearance, and intensity
110 with that obtained with solution B.

111 EC. About 0.1 g yields the reaction described for the identification of primary
112 aromatic amines under 2.1 General identification tests, producing a vivid red
113 precipitate.

114 D. Melting temperature, about 178°C.

115 **Sulfated ash.** Not more than 1.0 mg/g.

116 **Loss on drying.** Dry to constant weight at 105 °C; it loses not more than 15 mg/g.

117 **Related substances.** Carry out the test as described under *1.14.1 Chromatography*,
118 *High-performance liquid chromatography*, using a stainless steel column (25 cm x 4.6
119 mm) packed with end-capped particles of silica gel, the surface of which has been
120 modified with chemically-bonded octadecylsilyl groups (5 µm)¹.

121 Use the following conditions for gradient elution:

122 • Mobile phase A: water R.
123 • Mobile phase B: acetonitrile R.

<u>Time</u> <u>(Minutes)</u>	<u>Mobile phase A</u> <u>(% v/v)</u>	<u>Mobile phase B</u> <u>(% v/v)</u>	<u>Comments</u>
0 - 2	80	20	isocratic
2 - 17	80 to 75	20 to 25	linear gradient
17 - 40	75 to 20	25 to 80	linear gradient
40 - 41	20 to 80	80 to 20	return to initial composition
41 - 50	80	20	re-equilibration

124 Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet
125 spectrophotometer set at a wavelength of 254 nm.

126 Prepare the following solutions using as the diluent a mixture of 50 volumes of water
127 R and 50 volumes of acetonitrile R. For solution (1), dissolve 40 mg of the test
128 substance in 30 mL and dilute to 100.0 mL. For solution (2), dilute 1.0 mL of the
129 solution (1) to 100.0 mL. For solution (3), dilute 1.0 mL to 20.0 mL. For solution (4),
130 dissolve 2 mg of the test substance, 2 mg of 4-(4-aminobenzene-1-sulfonyl)phenol R
131 (impurity A), 2 mg of 4-(benzenesulfonyl)aniline R (impurity B) and 2 mg of 4,4'-
132 [oxybis[(4,1-phenylene)sulfonyl]]dianiline R (impurity C) and dilute to 50 mL. Dilute
133 1 mL of this solution to 10 mL.

134 Inject 20 µL each of solutions (1), (2), (3) and (4).

¹ An Thermo BDS Hypersil C18Column was found suitable.

135 Use the chromatogram obtained with solution (4) to identify the peaks due to
136 impurities A, B and C. The impurities, if present, are eluted at the following relative
137 retentions with reference to dapsoine (retention time about 10 minutes): impurity I
138 about 0.15; impurity A about 1.2; impurity G about 1.45; impurity D about 2.2;
139 impurity B about 2.4; impurity E about 3.0; impurity C about 3.2; impurity F about
140 3.45; and impurity H about 3.8.

141 The test is not valid unless, in the chromatogram obtained with solution (4), the
142 resolution between the peaks due to dapsoine and impurity A is at least 5.0. Also, the
143 test is not valid unless, in the chromatogram obtained with solution (3), the peak due
144 to dapsoine is detected with a signal-to-noise ratio of at least 10.

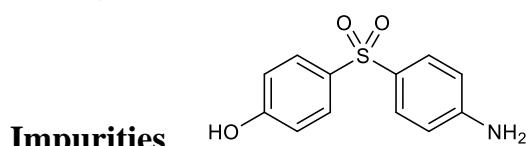
145 In the chromatogram obtained with solution (1):

- 146 • the area of any peak corresponding to impurity B, when multiplied by a
147 correction factor of 2.7, is not greater than 0.4 times the area of the peak due to
148 dapsoine in the chromatogram obtained with solution (2) (0.4 %);
- 149 • the area of any peak corresponding to impurity A, when multiplied by a
150 correction factor of 1.9, is not greater than 0.3 times the area of the peak due to
151 dapsoine in the chromatogram obtained with solution (2) (0.3 %);
- 152 • the area of any peak corresponding to impurity C, when multiplied by a
153 correction factor of 1.7, is not greater than 0.3 times the area of the peak due to
154 dapsoine in the chromatogram obtained with solution (2) (0.3 %);
- 155 • the area of any other impurity peak is not greater than 0.1 times the area of the
156 peak due to dapsoine in the chromatogram obtained with solution (2) (0.10 %).
- 157 • The sum of the areas of all impurity peaks, including the corrected areas of any
158 peaks corresponding to impurities A, B and C is not greater than the area of the
159 peak due to dapsoine in the chromatogram obtained with solution (2) (1.0%).
160 Disregard any peak with an area less than the area of the peak due to dapsoine
161 in the chromatogram in the chromatogram obtained with solution (3) (0.05%).

162 **Related substances.** Carry out the test as described under 1.14.1 Thin layer
163 chromatography, but using an unlined chamber, silica gel R3 as the coating substance,
164 and a mixture of 8 volumes of toluene R and 4 volumes of acetone R saturated with
165 water as the mobile phase. Apply separately to the plate 10 μ l of each of 5 solutions in
166 methanol R containing (A) 10 mg of the test substance per mL, (B) 10 mg of dapson RS per mL, (C) 0.15 mg of the test substance per mL, (D) 20 μ g of the test substance per mL and (E) 0.10 mg of 4,4'-thiodianiline RS per mL. The solution of 4,4'-thiodianiline RS should be freshly prepared. Pour the mobile phase into the chamber and insert the plate immediately, to avoid prior saturation of the chamber. After removing the plate from the chromatographic chamber, spray it with 4 dimethylaminocinnamaldehyde TS2. Heat the plate at 100°C and examine the chromatogram in daylight. The spot obtained with solution C is more intense than any spot obtained with solution A, other than the principal spot, and in addition, not more than 2 among those secondary spots are more intense than the spot obtained with solution D. Moreover, there is no visible spot corresponding in position and appearance with that obtained with solution E.

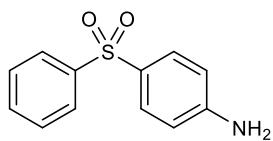
178 **Assay.** Carry out the assay as described under 2.7 Nitrite titration, using about 0.25
179 0.100 g, accurately weighed, dissolved in a mixture of 15 mL of water and 15 mL of
180 hydrochloric acid (~70 g/L) TS and titrate with sodium nitrite (0.1 mol/L) VS. Each
181 mL of sodium nitrite (0.1 mol/L) VS is equivalent to 12.42 mg of C₁₂H₁₂N₂O₂S.

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183



185 A. 4-(4-Aminobenzene-1-sulfonyl)phenol (synthesis related impurity),

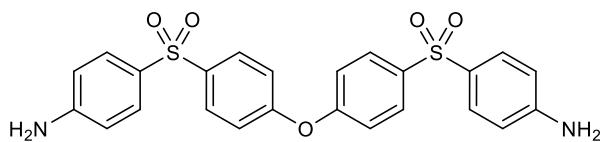
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188

189 B. 4-(Benzenesulfonyl)aniline (synthesis related impurity),

190



192

193 C. $1^4,7^4$ -Diamino-2 $\lambda^6,6\lambda^6$ -4-oxa-2,6-dithia-1,7(1),3,5(1,4)-
tetrabenzenaheptaphane-2,2,6,6-tetrone (synthesis related impurity),

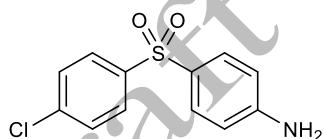
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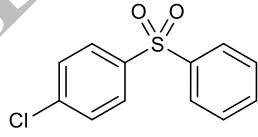
198 D. 2-(4-Aminobenzene-1-sulfonyl)aniline,

199



201

202 E. 4-(4-Chlorobenzene-1-sulfonyl)aniline,

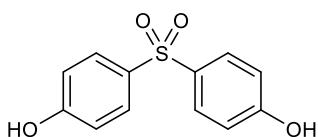


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205 F. 1-(Benzenesulfonyl)-4-chlorobenzene,

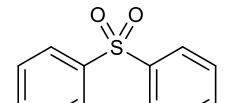
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209 G. 4,4'-Sulfonyldiphenol (synthesis related impurity),



210

211 H. 4,4' dichlorodiphenylsulfone (synthesis related impurity).

212 **Reagents to be established**

213 **4-(4-Aminobenzene-1-sulfonyl)phenol R**

214 $C_{12}H_{11}NO_3S$.

215 Molecular weight. 249.3

216 Description. Grey or light brown powder, hygroscopic, slightly soluble in methanol.

217 Melting point. About 138 °C.

218

219 **4-(Benzenesulfonyl)aniline R**

220 $C_{12}H_{11}NO_2S$.

221 Molecular weight. 233.3

222 Description. Light brown powder.

223 Melting point. About 176 °C.

224

225 **4,4'-[Oxybis[(4,1-phenylene)sulfonyl]]dianiline R**

226 $C_{24}H_{20}N_2O_5S_2$.

227 Molecular weight. 480.6

228 Description. Light brown powder.

229 Melting point. About 220 °C.

230

231 **Reference substances described**

232 **Dapsone RS**

233 ICRS already established. Intended uses to be adapted.

234

235

236

Draft for Comments