Promoting the
QUALITY OF MEDICINES Plus

Amoxicillin Job Aid to Assist with Dossier Preparation

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a five-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Contents

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Acronyms

ADE	acceptable daily exposure
API	active pharmaceutical ingredients
BP	The British Pharmacopeia
BW	body weight
CTD	common technical document
EP	The European Pharmacopeia
FPP	finished pharmaceutical product
HPLC	high performance liquid chromatography
MF	modifying factor
NMR	Nuclear Magnetic Resonance
NMT	no more than
NOAEL	no observable adverse effect level
NOEL	no observable effect level
OEL	occupational exposure limit
PK	pharmacokinetic factor
POD	point of departure
PQM+	Promoting the Quality of Medicines Plus
S	steady state
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
UF	uncertainty factor
UV	ultraviolet
V	volume

This document is a job aid for quick access to information to assist with dossier preparations for amoxicillin active pharmaceutical ingredients and finished products. The information consists of facilities, equipment, safety recommendations, and analytical data for production. The information herein is adapted from the Promoting Quality Medicines Program's Amoxicillin Product Information Report (July 2018).

Aid for CTD Module 2.3.A.1 – Facilities and Equipment

Table 1. Facilities for Processing Amoxicillin

Substance	Facility Needs
Amoxicillin	Dedicated facility preferred to avoid contamination, e.g., with penicillin

Table 2. Equipment for Formulating

Substance	Processing and Equipment
Amoxicillin trihydrate	**Dry granulation unit operations include:** Mills – for milling/cutting Sieves – for particle size distributions Blenders – double-cone blender, bin blender, or octagonal blender for blending Roller compactor – to form compacts Multi-mill or oscillatory granulator – for compacts converted to granulation Mixers – for mixing with extra-granular excipients Tablet presses – for tablet compressing Film coater – for applying film coating

Aid for CTD Module 2.5.5 – Safety

Table 3. Safety Recommendations for Employee Exposure

Area	Exposure Limits
Occupational exposure limit (OEL) – designed to be an 8-hour a day, 40-hour a week airborne concentration	OEL = NOEL (mg/kg/day) x BW (kg) / V (m^3/day) x S x UF x MF x **α** OEL = 2450 mg/kg/day x 70 kg / 10 m^3/day x 2 x 900 x 10 x 3 = 0.317 mg/m^3 = 320 µg/m^3 NOAEL = No observable adverse effect level UF = Uncertainty factors (6 for rat-to-human extrapolation, 10 for inter-human variation, 3 for sub-chronic to chronic extrapolation, 5 for available pre-clinical toxicity data) MF = Modifying factor of 10 for fatal anaphylactic reactions that may happen due to penicillin exposure S = Steady state based on elimination half-life = 2 α = pharmacokinetic factor based on bioavailability = 3 V = Volume of air breathed in a shift = 10 m^3

Table 4. Safety Control Band Recommendations for Employee Exposure

Area	Exposure Limits
Control band assignment: Category 2	>0.1 to 1 mg/m3 dust >5 to 50 ppm vapor Harmful on single exposure Use local exhaust ventilation
Acceptable daily exposure (ADE)	ADE = (POD mg/day) / UF_C x MF x PK ADE = 750 mg / 90 x 1 x 3 = 2.8 mg/day Where: POD = Point of departure BW = Body weight (kg) UF_C = (UF_A x UF_H x UF_S x UF_E x UF_R) UF_A = Interspecies UF_H = Intraspecies variability UF_S = Length of study UF_E = Severity of effect UF_R = Reference effect level MF = Modifying factor PK = Pharmacokinetic factor

Aid for CTD Module 3.2.S – Analytical Data for APIs

Table 6. API Physicochemical Properties

Analysis Type	Specification		
Appearance	White crystalline powder		
Crystal form	Diffraction Angle (2Θ)	d (Å)	Relative Intensity (%)
	12.17	7.27	35
	15.13	5.85	100
	16.25	5.45	22
	17.2	5.15	30
	18.04	4.91	91
	19.33	4.59	64
	19.77	4.49	36
	20.20	4.39	27
	21.48	4.13	39
	22.01	4.04	37
	22.46	3.96	23
	23.05	3.86	46
	23.49	3.79	58

Analysis Type	Specification
	23.82 3.73 21 25.75 3.46 65 26.69 3.34 61 27.1 3.29 23 27.9 3.2 20 28.71 3.11 73 29.47 3.03 54
Melting point	194 ºC
Optical rotation	+280 to +305° and +240 to +290°
Log P	0.87
pKa	pKa1 = 3.2 pKa2 = 11.7
Density	Bulk density = 0.15-0.45 g/mL Tapped density ≤ 1.2 g/mL
UV spectrum	λ_{max} = 230 nm 274 nm (ethanol) E = 10.85 (230 nm), 1.4 (274 nm) (ethanol)
Infrared spectrum	**Amoxicillin trihydrate** Wavenumbers cm^{-1} = 3520, 3458, 3046, 2964, 1775, 1686, 1580, 1517, 1482, 1396, 1378, 1327, 1314, 1283, 1250, 1143, 1120 **Amoxicillin sodium salt** Wavenumbers cm^{-1} = 3366, 2969, 1764, 1601, 1513, 1457, 1398, 1321, 1248, 1173, 1126
Nuclear magnetic resonance (NMR)	^{1}H-NMR Chemical shift (ppm) = 1.37, 1.42, 4.11, 4.52, 4.68 (all singlets); 5.36, 5.39 (quartet); 6.80, 7.19 (Double doublet) 13C-NMR Chemical shift (ppm) = 27.2, 31.1, 58.3, 58.7, 65.0, 67.4, 73.9, 116.8, 129.4, 131.4, 157.3, 175.2, 176.3
Mass spectrum	m/z (positive ion) = 349, 223, 160, 134, 122 m/z (negative ion) = 223

Table 7. IP, USP, BP, EP API Assay

Parameter	Specification				
Assay – Active pharmaceutical ingredients (API)	**API**	**IP 2014**	**USP**	**BP**	**EP**
	Amoxicillin (on anhydrous basis by HPLC)	85.0–100.5%	90.0–100.5%	89.0–102.0%	89.0–102.0%

Parameter	Specification			
	Amoxicillin trihydrate (on anhydrous basis by HPLC)	95.0–100.5%	95.0–100.5%	95.0–102.0%	95.0–102.0%

Aid for CTD Module 3.2.P – Analytical Data for FPPs

Table 8. IP, USP, BP, EP, FPP Assay

Parameter	Specification				
Assay – Finished product	**API**	**IP 2014**	**USP**	**BP**	**EP**
	Amoxicillin capsules	90.0–110.0%	90.0–120.0%	92.5–110.0%	N/A
	Amoxicillin tablets for oral suspension (Dispersible)	95.0–100.5%	95.0–100.5%	95.0–102.0%	95.0–102.0%
	Amoxicillin oral suspension (by HPLC)	90.0–120.0%	90.0–120.0%	80.0–120.0%	N/A
	Amoxicillin and potassium clavulanate injection (clavulanic acid)	90.0–107.0%	N/A	N/A	N/A
	Amoxicillin and potassium clavulanate oral suspension (clavulanic acid)	90.0–120.0% and 90.0–125.0%	90.0–120.0% and 90.0–125.0%	80.0–120.0%	N/A
	Amoxicillin and potassium clavulanate tablets (clavulanic acid)	90.0–120.0% and 90.0–120.0%	90.0–120.0% and 90.0–120.0%	90.0–105.0%	N/A
	Amoxicillin injection (by HPLC)	90.0–120.0%	90.0–120.0%	95.0–105.0%	N/A

Table 9. USP, BP, EP Related Substance and Degradation Product Assay

Substance	Specification			
Related substance and	**Related Substance**	**USP**	**BP**	**EP**
	Impurity J	N/A	NMT 3.0%	NMT 3.0%

Substance	Specification			
degradation products	Any other impurity	N/A	NMT 2.0%	NMT 2.0%
	Total impurities	N/A	NMT 9.0%	NMT 9.0%

Table 10. USP, BP, EP Amoxicillin Injection Assay by HPLC

Substance	Specification			
Amoxicillin injection	**Related Substance**	**USP**	**BP**	**EP**
	Amoxicillin dimer	N/A	NMT 3.0%	N/A
	Any other secondary peak	N/A	NMT 2.0%	N/A
	Sum of the areas of all the secondary peaks	N/A	NMT 9.0%	N/A

Table 11. USP, BP, EP Amoxicillin Trihydrate Injection Assay by HPLC

Substance	Specification			
Amoxicillin trihydrate	**Related Substance**	**USP**	**BP**	**EP**
		N/A		N/A
	Individual impurities: see Impurity Table	N/A	Any other impurity	N/A
				N/A

Table 12. USP, BP, EP Amoxicillin Capsules Assay by HPLC

Substance	Specification			
Amoxicillin capsules	**Related Substance**	**USP**	**BP**	**EP**
		Any secondary peak	NMT 1.5%	N/A
	No test for RS	Area of NMT secondary peak	NMT 1.0%	N/A
		Any other secondary peak	NMT 1.0%	N/A

Table 13. USP, BP, EP Amoxicillin and Potassium Clavulanate (oral suspension) Assay by HPLC

Substance	Specification			
Amoxicillin and potassium clavulanate oral suspension	**Related Substance**	**USP**	**BP**	**EP**
		Amoxicillin dimer	NMT 2.0%	
	N/A	Any other secondary peak	NMT 1.0%	

Table 14. USP, BP, EP Amoxicillin and Potassium Clavulanate (tablets) Assay by HPLC

Substance	Specification			
Amoxicillin and potassium clavulanate tablets	**Related Substance** N/A	**USP** Amoxicillin dimer Any other secondary peak	**BP** NMT 2.0% NMT 1.0%	**EP** N/A

Table 15. Amoxicillin Impurities by HPLC

Amoxicillin Related Compound	Relative Retention Time	Acceptance Criteria NMT (%)
I[a] (D-hydroxyphenylglycine)	0.32	1.0
D[b,c] (amoxicillin open ring)	0.53	1.0
	0.68	1.0
A[d] (6-aminopenicillanic acid)	0.78	0.5
B[e,f] (L-amoxicillin)	0.87	—
Amoxicillin	1.0	—
G[9] (D-hydroxyphenyl glycylamoxicillin)	2.9	1.0
E[h,i] (amoxicillin penilloic derivative)	4.5	1.0
MI (N-(penicillin-6-yl) open ring amoxicillinamide)	6.0	1.0
F[e,k] (phenylpyrazinediol)	6.3	—
C[l] (amoxicillin rearrangement product)	6.4	1.0
E[h,i] (amoxicillin penilloic derivative)	6.7	1.0
J[m] (amoxicillin open ring dimer)	8.8	1.0
L[n] (N-(penicillin-6-yl) amoxicillinamide)	9.0	1.0
Any unspecified individual impurity	—	1.0

[a](R)-2-Amino-2-(4-hydroxyphenyl)acetic acid. [b]The chromatographic system resolves two penicilloic acids from each other.

[c](4S)-2-{{(R)-2-Amino-2-(4-hydroxyphenyl)acetomido](carboxy)methyl)-5,5-dimethylthiazolidine-4-carboxylic acid.

[e]These compound are listed for information only and are not to be reported.

[l](4S)-2-{[R)-2-Amino-2-(4-hydroxyphenyl)acetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid. [l](2S,5R,6R)-6-(2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-((4S)-4-carboxy-5,5-dimethylthiazolidin-2yl)acetamido)-3,3-

dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. [k]3-(4-hydroxyphenyl)pyrazin-2-ol. [l](4S)-2-[5-(4-hydroxyphenyl)-3,6-dioxopiperazin-2yl]-5,5-dimethylthiazolidine-4-carboxylic acid. [m](2S,5R,6R)-6-((2R)-2-{2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamidol]-2-{(4S)-4-carboxy-5,5dimethylthiazolidin-2yl]actamidol}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid.

[n](2S,5R,6R)-6-{(2S,5R,6R)-6-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia1azabicyclo{3.2.0]heptane-2-carboxamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2carboxylic acid.

References

Web site
usp-pqm.org. Promoting Quality Medicines Product Information Report-Amoxicillin [July 2018] Available from: https://www.usp-pqm.org/sites/default/files/pqms/article/amoxicillin-pir-jul2018.pdf