Health Canada Santé Canada

Veterinary Drugs Directorate (VDD)
Health Products and Food Branch (HPFB)

Certified Product Information Document (CPID) - VDD

Introduction

(a) Summary of product information:

Proprietary (brand) name of drug product	AQUAFLOR®
Proper or common name of drug product	Florfenicol
Proper or common name of drug substance (active ingredient)	Florfenicol
Manufacturer name (fabricator)	Merck Animal Health
Manufacturer name (sponsor)	Intervet Canada Corp.
Therapeutic classification	Antibiotic
Dosage form(s)	Drug premix
Strength(s)	50 % florfenicol
Route of administration	Oral
Type of submission	NC

(b) Administrative summary:

Dossier ID number	HC6-024-v155241
Control number (DSTS Number)	268763
Sponsor's date of preparation or revision	2023-08-21
Revision number (for sponsor use)	2023-08-21 (Level III 2023-043, 2023-030, 2023-073; Level IV 2022-048, 2023-088)

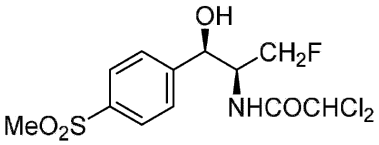
6.3 Drug substance

Note: Include the information on the drug substance in the open part of the Master File (MF) in the appropriate sections.

6.3.1 General information

6.3.1.2 Chemical structure *(NC, DSTS 268763, part 2.2.S DMF AP section 3.2.S.1.2)*

(a) Structural formula, including relative and absolute stereochemistry:



(b) Molecular formula:

$C_{12}H_{14}Cl_2FNO_4S$

(c) Molecular mass:

358.2 g/mol

6.3.1.3 Physicochemical properties *(NC, DSTS 268763, part 2.2.S DMF AP section 3.2.S.1.3)*

(a) Physical form (for example [e.g.], polymorphic form, solvate, hydrate):

White to off-white crystalline powder.

(b) Solubilities and Dose/Solubility Volume over the physiological pH range (1.2-6.8):

Minsheng:
Freely soluble in acetone; soluble in methanol; sparingly soluble in ethanol; slightly soluble in water.

Apeloa:
Practically insoluble in water; very soluble in dimethylformamide; sparingly soluble in glacial acetic acid; slightly soluble in chloroform.

(c) pK_a:

9.03

6.3.2 Method of manufacture

6.3.2.1 Fabricator(s) *(NC, DSTS 146176, response to MIR #2; NC, DSTS 268763, part 2.2.S DMF AP section 3.2.S.2.1 and part 2.2.S.2.1)*

(a) Name, address, and responsibility of each fabricator, including contractors, and each production site or facility involved in fabrication and testing of the drug substance:

Site	Responsibility
Minsheng Group Shaoxing Pharmaceutical Co. Ltd. 315 Tanggong Road, Paojiang Industrial Zone, Shaoxing, Zhejiang, China, 312071 *DEL 100147-A*	Manufacturing, Packaging, Release and stability testing (all tests)
Zhejiang Apeloa Jiayuan Pharmaceutical Co., Ltd. 519 Jiangnan road, Hengdian Industrial Zone, Dongyang, Zhejiang, China, 322118 *DEL 100147-A* [1]	Manufacturing Packaging Release and stability testing (all tests)
Vet Pharma Friesoythe GmbH Sedelsberger Strasse 2-4, Friesoythe, Niedersachsen, Germany, 26169 *DEL 100147-A*	Release testing (all tests)
Merck Animal Health 2667 West Dual Street, Baton Rouge, Louisiana, United States, 70814-4906 *DEL 100147-A*	Release testing (all tests)
Intervet GesmbH Siemensstrasse 107, Vienna, Austria, 1210 *DEL 100147-A*	Release testing (Description and Identification by IR only)

DEL = Drug Establishment Licence

[1] The microbial testing activity is not currently on the DEL for Apeloa since it was not considered to be covered by the last inspection report. Friesoythe will completely retest all batches for microbial testing until the activity is included on the DEL.

(b) List of referenced DMFs and MF Numbers or CEP Number, if applicable:

Minsheng:
MF: Type II VMF-005-913, version 2023-05-19
CEP: No CEP is available.

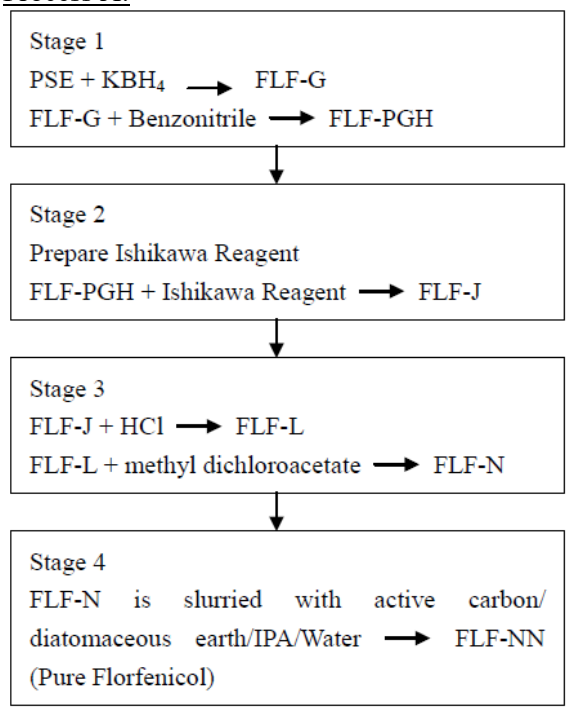
Apeloa:
MF: Canada MF 1.0 (July 2022), VDD MF # f2022928
CEP: No CEP is available.

6.3.2.2 Description of Manufacturing Process and process controls *(NC, DSTS 268763, part 2.2.S DMF AP section 3.2.S.2.2)*

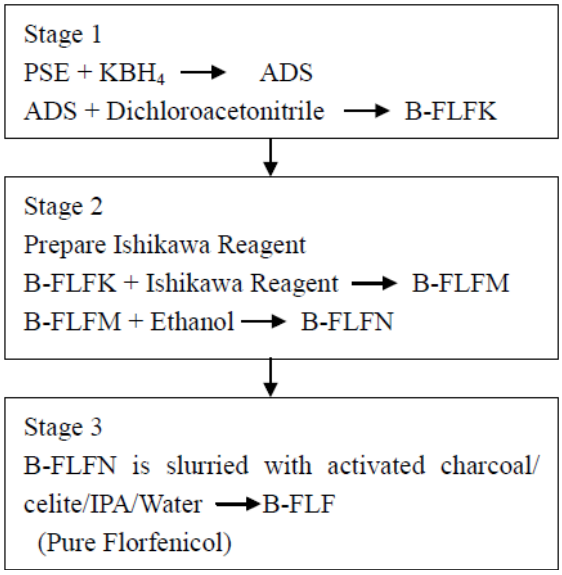
(a) Flow diagram showing reactants, solvents and reagents:

Minsheng:

Process A:

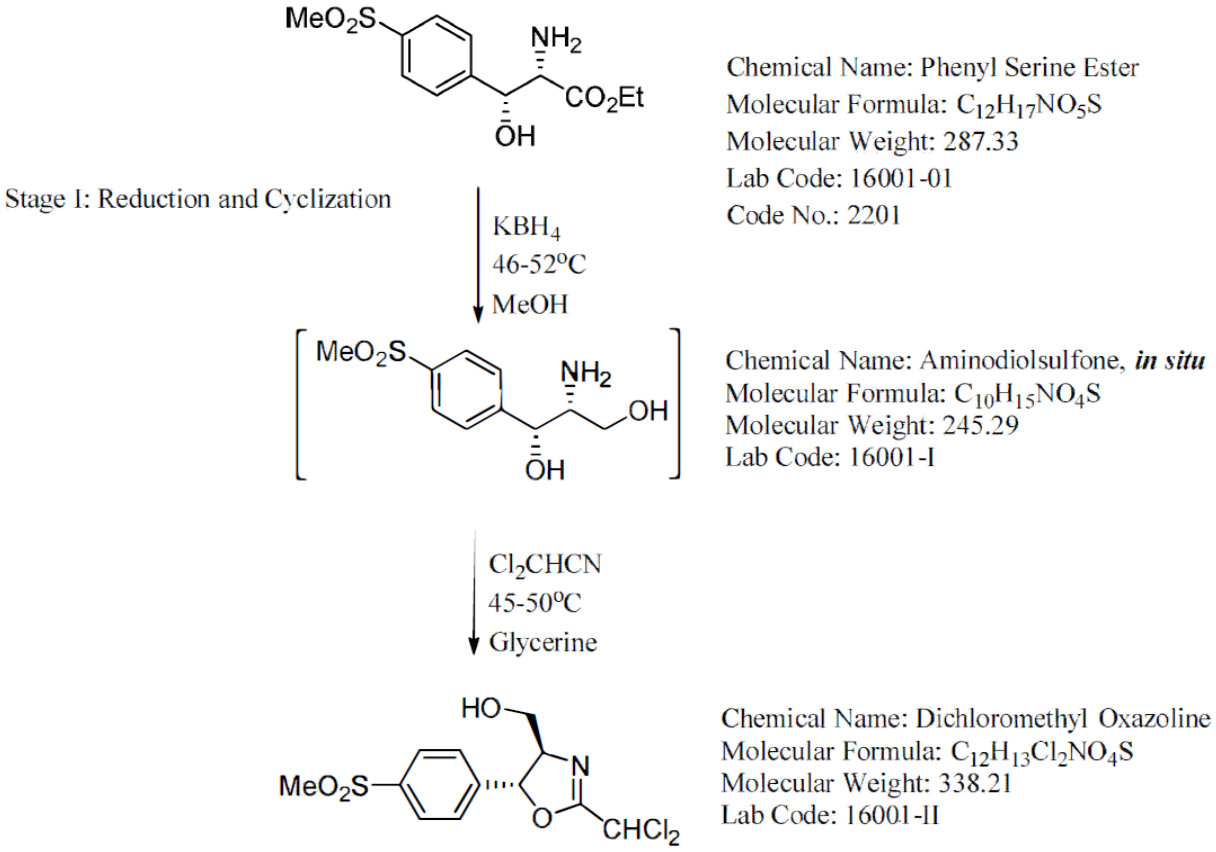


Process B:



Apeloa:

Process B:



Chemical Name: Phenyl Serine Ester
Molecular Formula: $C_{12}H_{17}NO_5S$
Molecular Weight: 287.33
Lab Code: 16001-01
Code No.: 2201

Chemical Name: Aminodiolsulfone, ***in situ***
Molecular Formula: $C_{10}H_{15}NO_4S$
Molecular Weight: 245.29
Lab Code: 16001-I

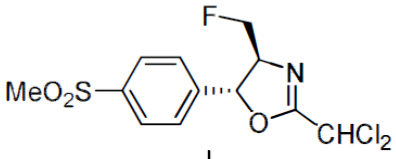
Chemical Name: Dichloromethyl Oxazoline
Molecular Formula: $C_{12}H_{13}Cl_2NO_4S$
Molecular Weight: 338.21
Lab Code: 16001-II

Stage II: Fluorination

Ishikawa Reagent ← $C_4H_{11}N + C_3F_6$

100-108°C,0.6-0.8Mpa

DCM/MeOH/CH_3COONa

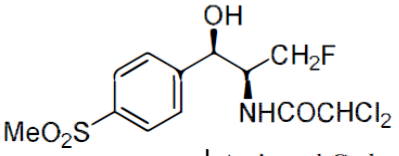


Chemical Name: Dichloromethylfluoro Oxazoline
Molecular Formula: $C_{12}H_{12}Cl_2FNO_3S$
Molecular Weight: 340.20
Lab Code: 16001-III

Stage III: Hydrolysis

IPA/H_2O

80-85°C



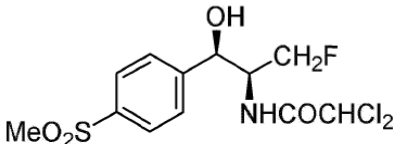
Chemical Name: Crude Florfenicol
Molecular Formula: $C_{12}H_{14}Cl_2FNO_4S$
Molecular Weight: 358.21
Lab Code: Crude 16001

Stage IV: Purification

Activated Carbon

IPA/H_2O

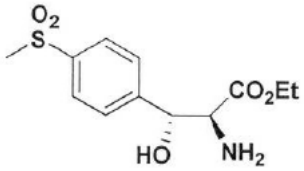
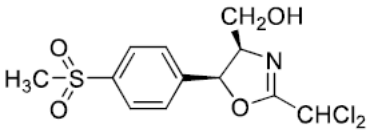
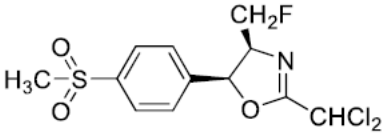
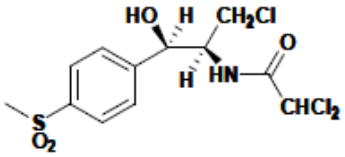
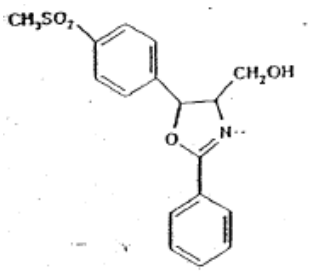
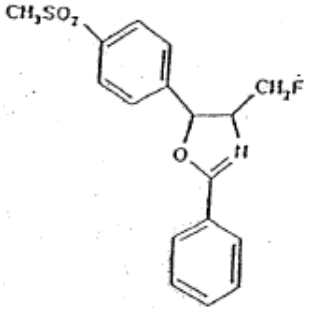
80-85°C

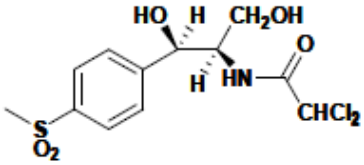
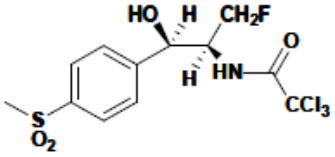
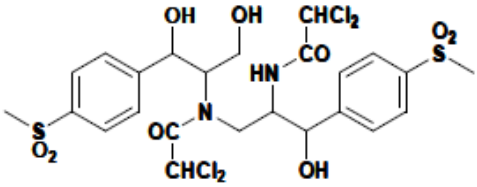
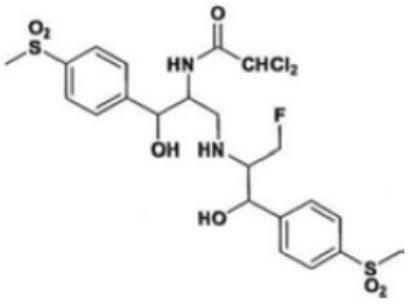
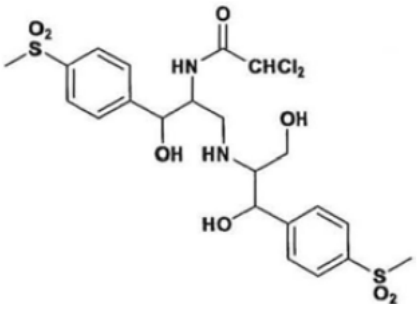
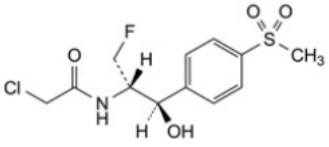


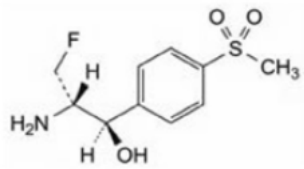
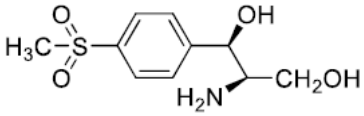
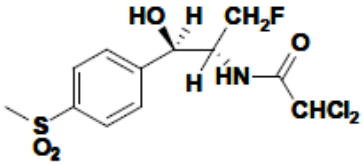
Chemical Name: Florfenicol
Molecular Formula: $C_{12}H_{14}Cl_2FNO_4S$
Molecular Weight: 358.21
Lab Code: 16001

6.3.4 Impurities *(NC, DSTS 268763, part 2.2.S DMF AP section 3.2.S.3.2)*

Potential impurities not routinely controlled in the drug substance:

Potential impurities	Chemical name	Chemical structure	Minsheng		Apeloa
			Process A	Process B	Process B
PSE (16001-01, starting material)	D-P-Methyl Sulfone Phenyl Ethyl Serinate		✓	✓	✓
Dichloremethyl oxazoline (16001-II, intermediate)	((4R,5S)-2-(dichloromethyl)-5-(4-(methyl sulfonyl) phenyl)-4, 5-dihydrooxazol-4-yl) methanol			✓	✓
16001-III (intermediate)	(4S,5S)-2-(dichloromethyl)-4-(fluoro methyl)-5-(4-(methyl sulfonyl) phenyl)-4,5-dihydrooxazole			✓	✓
Chloro analogue	2,2-dichloro-*N*-[(l*R*,2*S*)-3-chloro-l -hydroxy-1-[4-(methylsulfonyl) phenyl] propan-2-yl] acetamide		✓	✓	
Oxazoline sulfone	(5-(4-(methylsulfonyl)phenyl)-2-phenyl-4,5-dihydrooxazol-4-yl)methanol		✓		
Fluorazoline	4-(fluoromethyl)-5-(4-(methylsulfonyl)phenyl)-2-phenyl-4,5-dihydrooxazole		✓		

Potential impurities	Chemical name	Chemical structure	Minsheng		Apeloa
			Process A	Process B	Process B
Impurity A (Thiamphenicol)	2,2-dichloro-*N*-[(1*R*,2*R*)-l,3-dihydroxy-1-[4-(methyl sulfonyl) phenyl] propan-2-yl] acetamide		✓	✓	✓
Impurity B (Trichloro acetamide analog)	2,2,2-trichloro-*N*-[(l*R*,2*S*)-3-fluoro-l -hydroxy-1-[4-(methylsulfonyl) phenyl] propan-2-yl] acetamide		✓	✓	✓
Impurity C (Related compound 1)	2,2-dichloro-*N*-[2-[(2,2-dichloroacety l)amino]-3-hydroxy-3-[4-(methyl sulfonyl)phenyl]propyl]-*N*-[1,3-dihydroxy-1-[4-(methylsulfonyl) phenyl]propan-2-yl]acetamide		✓	✓	✓
Impurity D (Related compound 2)	2,2-dichloro-N-[3-[[3-fluoro-1-hydroxy-1-[4-(methylsulfonyl) phenyl]propan-2-yl] amino]-1-hydroxy-1-[4-(methylsulfonyl) phenyl]propan-2-y] acetamide		✓	✓	✓
Impurity E (Related compound 3)	2,2-dichloro-N-[3-[[1,3-dihydroxy-1-[4-(methylsulfonyl) phenyl]propan-2-yl]amino)-1-hydroxy-1-[4-(methylsulfonyl) phenyl] propan-2-yl]acetamide		✓	✓	✓
Impurity F (Monochloro acetamide analog)	2-chloro-N[(1R,2S)-3-fluoro-1-hydroxy-1- [4-(methane sulfonyl) phenyl] propan-2-yl] acetamide		✓	✓	✓

Potential impurities	Chemical name	Chemical structure	Minsheng		Apeloa
			Process A	Process B	Process B
Impurity G (Florfenicol amine)	(1R,2S)-2-amino-3-fluoro-1-[4-(methane sulfonyl) phenyl] propan-1-ol		✓	✓	✓
Impurity H (16001-I, Thiamphenicol amine, intermediate)	(1R,2R)-2-amino-1- [4-(methane sulfonyl) phenyl] propane-1,3-diol		✓	✓	✓
Impurity I (Erythro isomer)	2,2-dichloro-N-[(1S,2R)-3-fluoro-1-hydroxy-1-[4-(methanesulfonyl) phenyl] propan-2-yl] acetamide		✓	✓	✓

6.3.5 Control of the drug substance

6.3.5.1 Specification *(NC, DSTS 158548, part 2.2.S.5.1; NC, DSTS 268763, parts 2.2.S.5.1 and 2.2.S.5.2)*

(a) Specification(s) for the drug substance (including specification number and version, as well as test method number(s) and version(s) are required:

Baton Rouge - Minsheng:

Standard claimed (e.g., Professed, USP, Ph. Eur., BP, other)		Professed
Specification approved date		2014-06-01
Specification and Analytical methods reference number and version		02TE0086 edition 06
Test	Acceptance Criteria	Analytical Procedure (Type/Source/Version)
Appearance	White to off-white powder; free from foreign matter	Visual / House / Minsheng: MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0
Identification by IR	The IR spectrum of the Sample agrees with IR spectrum of the Standard	IR / House / Minsheng: MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0
Identification by TLC	The Sample chromatogram corresponds to the Standard chromatogram	TLC / House / Minsheng: MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0
Related compounds by TLC	Individual ≤ 1 % Total ≤ 3.0 %	
Optical rotation	$[\alpha]^{25}_{D}$ = -15° to -20°	Polarimeter / Minsheng: USP <781> Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0 (refers to USP <781>)
pH	4.5 to 7.0	Minsheng: USP <791> Friesoythe: House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Water	≤ 0.5 %	Karl Fischer / House / Minsheng: MF Friesoythe: House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Residue on Ignition	≤ 0.2 %	Minsheng: House / MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0 (refers to USP <281>)

Standard claimed (e.g., Professed, USP, Ph. Eur., BP, other)		Professed
Specification approved date		2014-06-01
Specification and Analytical methods reference number and version		02TE0086 edition 06
Test	Acceptance Criteria	Analytical Procedure (Type/Source/Version)
Heavy Metals	≤ 20 ppm	Minsheng: House / MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0 or 04-FRI-0092-M-02 Revision 00 (identical to former USP <231> Method II)
Melting range	152 to 157°C	Minsheng: USP <741> Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0
Related compounds by HPLC	Individual: Thiamphenicol ≤ 0.2 % Trichloroacetamide analog ≤ 0.3 % Related compound 1 ≤ 0.3 % Related compound 2 ≤ 0.3 % Related compound 3 ≤ 0.3 % Other (each) ≤ 0.20 % Total: ≤ 1.0 %	HPLC / House / Minsheng: MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0
Assay by HPLC	98.0 to 102.0 %	
Residual solvent	Isopropyl alcohol: ≤ 0.2 %	GC / House / Minsheng: MF Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0
Microbial limits	Total Viable Aerobic Count < 100 cfu/g	Microbial / Minsheng: House / MF Friesoythe: USP <61>, Ph. Eur 2.6.12
Bacterial Endotoxins [1]	≤ 0.06 EU/mg	LAL / USP <85>, Ph. Eur 2.6.14

[1] Test not applicable for florfenicol used in the AQUAFLOR product.

Vienna - Minsheng:

Standard claimed (e.g., Professed, USP, BP, Ph.Eur., other)		Professed
Specification approved date		2022-09-07
Specification reference number and version		SPM-265DE, REV05
Test	Acceptance Criteria	Analytical Procedure (Type/Source/Version)
Appearance	White to off-white powder; free from foreign matter	Visual / House / Friesoythe: 02-FRI-011999-RPV-03-EZ Revision 0.0 Vienna: SPM-265DE, REV05
Identification by IR	Complies with requirements	IR / Friesoythe: House / 02-FRI-011999-RPV-03-EZ Revision 0.0 Vienna: SPM-265DE, REV05 (refers to USP <197>)
Optical rotation	$[\alpha]^{25}_{D}$ = -15° to -20°	Polarimeter / House / 02-FRI-011999-RPV-03-EZ Revision 0.0 (refers to USP <781>)
pH (25°C)	4.5 to 7.0	House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Residue on Ignition	≤ 0.2 %	02-FRI-011999-RPV-03-EZ Revision 0.0(refers to USP <281>)
Assay by HPLC	98.0 to 102.0 %	HPLC / House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Related compounds by HPLC	Individual: Thiamphenicol ≤ 0.2 % Trichloroacetamide analog ≤ 0.3 % Related compound 1 ≤ 0.3 % Related compound 2 ≤ 0.3 % Related compound 3 ≤ 0.3 % Other (each) ≤ 0.20 % Total ≤ 1.0 %	
Related compounds by TLC	Individual ≤ 1.0 % Total ≤ 3.0 %	TLC / House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Heavy Metals	≤ 20 ppm	House / 02-FRI-011999-RPV-03-EZ Revision 0.0 or 04-FRI-0092-M-02 Revision 00 (identical to former USP <231> Method II)
Melting Range	152°C to 157°C	House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Water	≤ 0.5 %	Karl Fischer / House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Residual solvent	lsopropyl alcohol ≤ 0.2 %	GC / House / 02-FRI-011999-RPV-03-EZ Revision 0.0
Microbial limits	Total Viable Aerobic Count < 100 cfu/g	Microbiological / USP <61>, Ph. Eur 2.6.12

Vienna - Apeloa:

Standard claimed (e.g., Professed, USP, BP, Ph.Eur., other)		Professed
Specification approved date		2022-08-11
Specification reference number and version		SPM-304DE, REV03
Test	Acceptance Criteria	Analytical Procedure (Type/Source/Version)
Appearance	White to off-white powder; free from foreign matter	Visual / House / Friesoythe: 02-FRI-366289-RPV-02-EZ Rev.0.0 Vienna: SPM-304DE, REV03
Identification by IR	Complies with requirements	IR / Friesoythe: House / 02-FRI-366289-RPV-02-EZ Rev.0.0 Vienna: SPM-304DE, REV03 (refers to USP <197>)
Enantiomeric purity	Impurity I ≤ 0.30 %	HPLC / House / 02-FRI-366289-RPV-02-EZ Rev.0.0
pH (25°C)	4.5 to 7.0	House / 02-FRI-366289-RPV-02-EZ Rev.0.0
Residue on Ignition	≤ 0.2 %	02-FRI-366289-RPV-02-EZ Rev.0.0 (refers to USP <281>)
Assay	98.0 to 102.0 %	HPLC / House / 02-FRI-366289-RPV-02-EZ Rev.0.0
Related compounds by HPLC	Individual: Thiamphenicol ≤ 0.20 % Trichloroacetamide analog ≤ 0.20 % Related compound 1 ≤ 0.20 % Related compound 2 ≤ 0.20 % Related compound 3 ≤ 0.20 % Other (each) ≤ 0.20 % Total ≤ 1.0 %	
Heavy Metals	≤ 20 ppm	House / 02-FRI-366289-RPV-02-EZ Rev.0.0 or 04-FRI-0092-M-02 Revision 00 (identical to former USP <231> Method II)
Melting Range	152°C to 157°C	House / 02-FRI-366289-RPV-02-EZ Rev.0.0
Water	≤ 0.5 %	Karl Fischer / House / 02-FRI-366289-RPV-02-EZ Rev.0.0
Residual solvent	lsopropyl alcohol: ≤ 2000 ppm	GC / House / 02-FRI-366289-RPV-02-EZ Rev.0.0
Microbial limits	Total Viable Aerobic Count < 100 cfu/g	Microbial / USP <61>, Ph. Eur 2.6.12

6.3.7 Packaging *(volume/page)*

(a) Description of the container closure system(s) including materials of construction:

Minsheng:
Double polyethylene bags (tie closures) within fiberboard drums fitted with steel lids.
Seals are applied to the bag ties and the drum seal.

Apeloa:
Fiberboard drums with double polyethylene (PE) bags preventing contact with the fiberboard drums and acting as airtight seal to exclude air and moisture. The two PE bags are respectively tied with nylon bag ties.
The fiberboard drums are tightly covered with fiberboard or metal lid after packaging, the closure is made up of a round metal ring which holds together the drum and lid, and is fixed to the lid and sealed. The lock seal is "V" shaped with "AL" emblem, which will be broken once the drum is opened.

6.3.8 Stability

6.3.8.2 Accelerated and long term studies *(NC, DSTS 268763, part 2.2.S DMF AP sections 3.2.S.6 and 3.2.S.7.3)*

(a) Storage conditions and retest period (or shelf life, where appropriate):

Minsheng:

Container Closure System	Storage Conditions	Re-test Period
Refer to 6.3.7(a)	Below 30 ºC, with excursions permitted up to 40°C	Process A: 36 months
		Process B: 24 months

Apeloa:

Container Closure System	Storage Conditions	Re-test Period
Refer to 6.3.7(a)	Preserve in tight containers, and store at temperature below 30°C.	36 months

6.4 Drug product

6.4.1 Description of the drug product *(volume/page)*

(a) Description of the drug product:

Aquaflor® is a 50 % (w/w) medicated premix for inclusion into fish feed. It contains the synthetic broad spectrum antibiotic, florfenicol.

The product is indicated for the treatment of furunculosis caused by susceptible strains of *Aeromonas salmonicida* in salmon. It can be mixed in un-medicated fish feed prior to pelleting or surface coated on pellets. It should be added to feed to deliver 10 mg florfenicol per kg body weight daily for 10 consecutive days.

(b) Description of each type of container/closure system to be used for the drug product (including rubber stopper supplier and formulation number for injectable products):

Refer to 6.4.5.1(a)

(c) Storage conditions and expiration period (including in-use storage conditions and in-use storage period, if applicable):

Storage conditions:	Store in a dry place between 2°C and 30°C. Use premix within 12 months of opening pouch. Use medicated feed not more than 6 months after manufacture. Keep separate from other feeds.
Expiration period:	36 months

(d) Description of accompanying reconstitution diluent(s), if applicable:

Not applicable

(e) Description of each type of container/closure system used for the accompanying reconstitution diluent, if applicable:

Not applicable

(f) Description of accompanying dosing devices, if applicable:

Not applicable

6.4.3 Method of manufacture

6.4.3.1 Fabricator(s) *(NC, DSTS 194780, part 2.2.P.3.1; NC, DSTS 268763, part 2.2.P.3.1)*

(a) Name, address, and responsibility of each site, including contract sites, involved in the fabrication, packaging, labelling, testing, importing/release, storage, and distribution of the drug product:

Site	Responsibility
Merck Animal Health 2667 West Dual Street, Baton Rouge, Louisiana, United States, 70814-4906 *DEL 100147-A*	Manufacturing, Filling and Packaging, Release and stability testing (all tests)
Delpharm Montréal Inc. (formerly Famar Montréal Inc. 3535 route Transcanadienne, Pointe-Claire, Quebec, Canada, H9R 1B4 *DEL 3-002681-A*	Release testing (all tests)
Intervet GesmbH Siemensstrasse 107, Vienna, Austria, 1210 *DEL 100147-A*	Manufacturing Packaging Release and stability testing (all tests)
Neopharm Labs Inc. 865 Michele-Bohec Boulevard, Blainville, Quebec, Canada, J7C 5J6 *DEL 101992-B*	Release testing (all tests)
Merck Canada Inc. 16750 route Transcanadienne, Kirkland, Quebec, Canada, H9H 4M7 *DEL 101380-A*	QA release oversight
Intervet Canada Corp. 16750 route Transcanadienne, Kirkland, Quebec, Canada, H9H 4M7 *DEL 100147-A*	Importer and Distributor

DEL = Drug Establishment Licence

6.4.3.2 Formulae

6.4.3.2.1 Quantitative formula *(NC, File 9460-S0007-520, Control No. 2005101C; NC, DSTS 268763, parts 2.2.P.3.2 and 2.2.P.3.3.2)*

(a) Composition, i.e., list of all components of the dosage form, and their amounts on a per unit basis:

Component and Quality Standard (e.g., USP, BP, Ph. Eur., other)	Function	Strength (label claim)	
		50 % florfenicol	
		Quantity per unit	% (w/w)
Florfenicol (Professed)	Active	500 g/kg	50 %
Lactose monohydrate (Ph. Eur., NF)	Matrix compound	470 g/kg	47 %
Povidone K29/32 (Ph. Eur., USP)	Binder	30 g/kg	3 %
Purified water [a]	Granulation processing aid	- [a]	- [a]
Total	-	1000 g/kg	100 %

[a] Purified water is added for granulation but is evaporated during drying.

(b) Composition of all components that are mixtures (e.g., colourants, coatings, capsule shells, imprinting inks):

Not applicable

6.4.3.2.2 Batch formula *(NC, File 9460-S0007-520, Control No. 2005101C; NC, DSTS 268763, parts 2.2.P.3.2 and 2.2.P.3.3.2)*

(a) List of all components of the dosage form to be used in the fabrication process, and their amounts on a per batch basis, including those removed during the production process.

Note: Indicate the use of overages and justification, if applicable.

Manufacturing site	**Baton Rouge**	**Vienna**	
Strength (label claim)	50 % florfenicol		
Master Production Document reference #, version #	Mixing Record effective 2018-12-13	MBR-044D-Aquaflor 50%, REV04	MBR-064D-Aquaflor 50%_600kg, REV06
Batch size(s) (number of dosage units)	258 lbs (117.3 kg)	300 kg	600 kg
Component and Quality Standard (e.g., USP, BP, Ph. Eur., other)	Quantity per batch	Quantity per batch	Quantity per batch
Florfenicol (Professed) [a]	129.00 lbs	150.000 kg	300.00 kg
Lactose monohydrate (Ph. Eur., NF)	121.26 lbs	141.000 kg	282.00 kg
Povidone K29/32 (Ph. Eur., USP)	7.74 lbs	9.000 kg [c]	18.000 kg [c]
Purified water (Ph. Eur.) [b]	31 lbs [b]	38.33 kg [b]	64.7 kg [b]
Total	258 lbs	300.0 kg	600.0 kg

[a] Quantity of the active is adjusted based on the assayed purity of the florfenicol, if less than 100 %.

[b] Purified water is added for granulation but is evaporated during drying. Purified water is not contained in the finished drug product. Its quantity to be used may vary within predefined ranges depending on evaporation losses and recovery of fine fraction

[c] An excess of granulation solution needs to be prepared for filling the hoses (dead volume):

For the 300 kg batch size: 11.500 kg povidone will be dissolved in 38.33 kg water, in total 49.830 kg granulation solution will be prepared. It is guaranteed that only 9.000 kg povidone will be added to pre-mix.

For the 600 kg batch size: 19.320 kg povidone will be solved in 64.7 kg water, in total 84.02 kg granulation solution will be prepared. It is guaranteed that only 18.000 kg povidone will be added to pre-mix.

Master Packaging document:

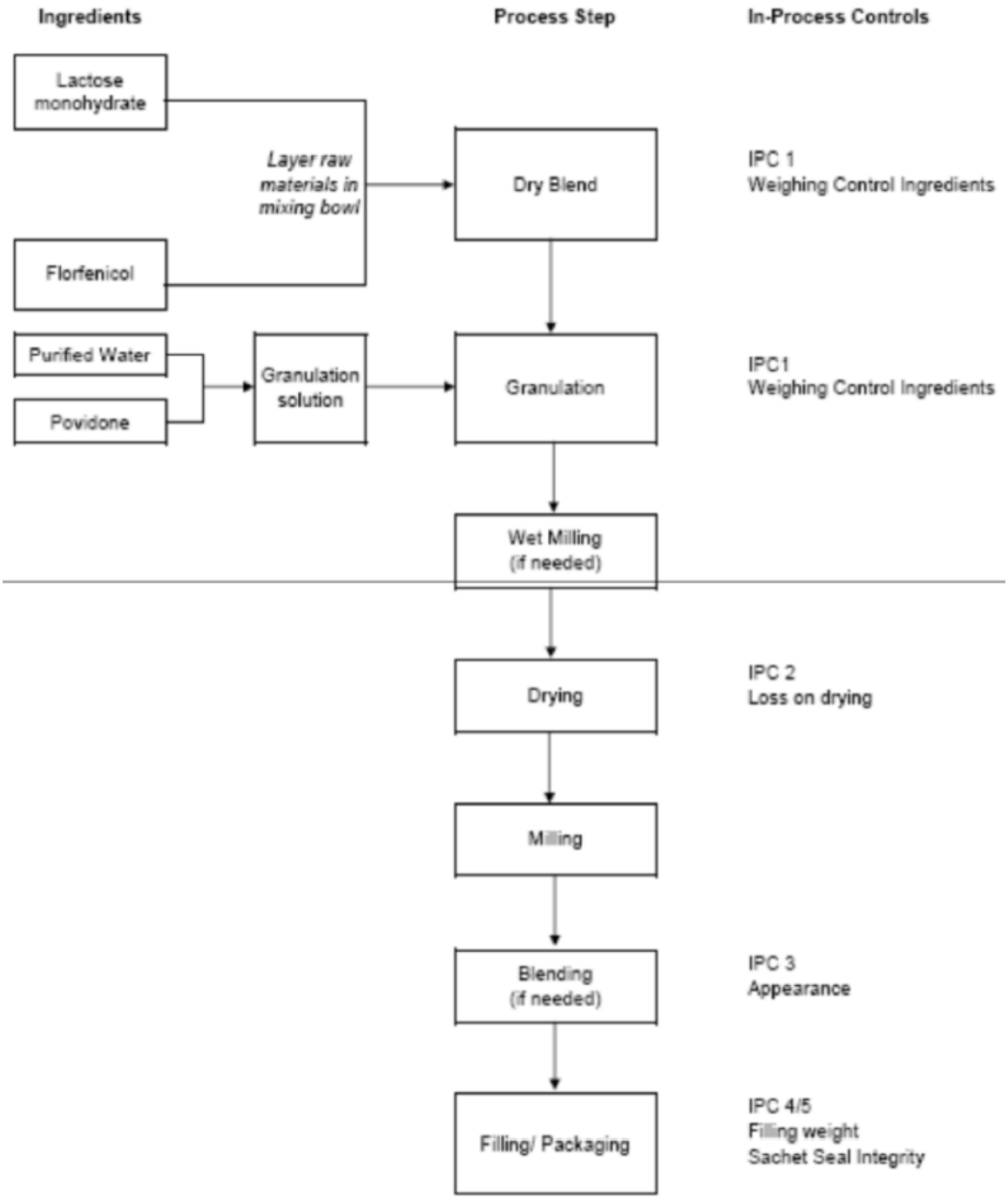
Baton Rouge: Pouch filling instructions 136255 effective 2016-04-29
Vienna: BPR-050D, REV03

6.4.3.3 Manufacturing process

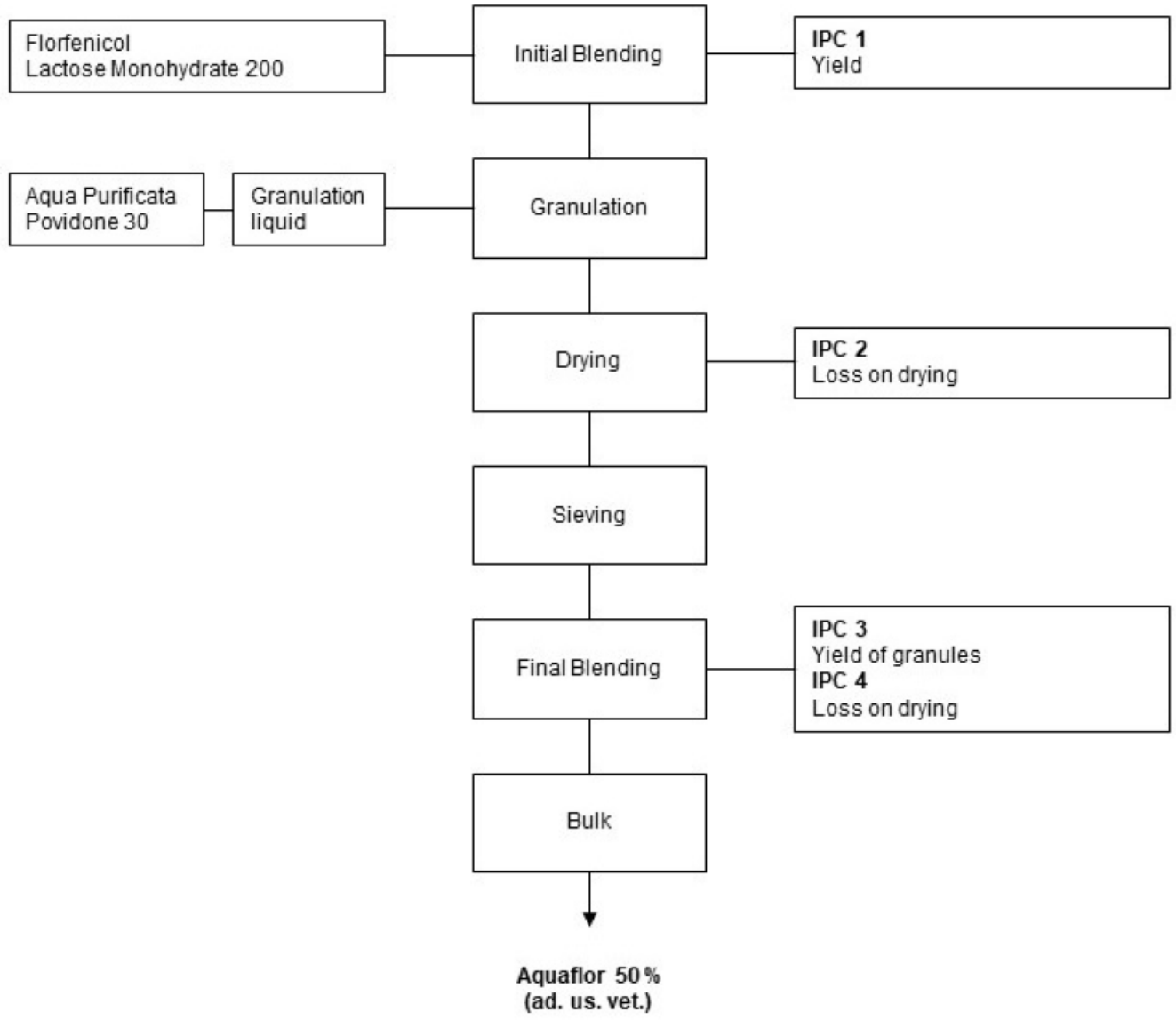
6.4.3.3.1 Description *(NC, DSTS 268763, parts 2.2.P.2, 2.2.P.3.3.1, 2.2.P.3.3.2 and 2.2.P.3.4.2)*

(a) Flow diagram of the manufacturing process:

Baton Rouge:



Vienna:


Florfenicol
Lactose Monohydrate 200
Initial Blending
IPC 1
Yield
Aqua Purificata
Povidone 30
Granulation liquid
Granulation
Drying
IPC 2
Loss on drying
Sieving
Final Blending
IPC 3
Yield of granules
IPC 4
Loss on drying
Bulk
Aquaflor 50 %
(ad. us. vet.)

(b) Narrative summary of the fabrication process, including amounts of ingredients, equipment type, process parameters, in-process testing with acceptance criteria:

Baton Rouge:

Manufacturing narrative summary:

1. Dissolve the povidone in 14 kg of purified water in a suitable vessel while mixing with an agitator.
2. Charge into the Gral bowl; about half the amount of florfenicol, about half the amount of lactose monohydrate, the remaining florfenicol, and the rest of the lactose monohydrate. Blend the ingredients.
3. Add the povidone solution from Step 1 to the powder blend from Step 2 at a steady flow rate while continuing mixing at slow speed. Granulate batch at fast speed, then include high shear mixing action (chopper). Add additional purified water as necessary, to achieve a suitable granulation.
4. If necessary, mill the damp granulation through a hammer mill fitted with a stainless steel screen at slow speed knives forward. Transfer the granulation to a fluid bed dryer.
5. Dry the granules for approximately 30 minutes and check the Loss on drying (LOD) before continuing drying.
   Dry to a moisture content of ≤ 1.2 % LOD.
6. Pass the dried granules through a hammer mill fitted with a round hole screen at medium speed, knives forward.
7. If necessary, blend the bulk powder in a tumble blender.

Equipment:

- Stainless steel Vessel with agitator
- High Shear Mixing Granulator (Mixer / Chopper)
- Fluidized Bed Dryer
- Hammer Mill
- Powder suction conveyer
- Automated packaging machine

Vienna:

Manufacturing narrative summary:

1. The florfenicol and lactose monohydrate are weighed into an intermediate bulk container and then mixed in this container until homogenous.
2. Povidone is dispensed in the required amount of water for the preparation of the granulation liquid.
3. Each of the following process steps is performed three times because the full batch is processed as three sublots:
    - Suction of one third of initial blend into the granulator (100 kg for the 300 kg batch size and 200 kg for the 600 kg batch size)
    - Addition of the granulation liquid (13 kg for the 300 kg batch size and 26 kg for the 600 kg batch size)
    - Granulation
    - After complete granulation sieving of the wet granulate sublots into the fluid bed dryer.
    - Drying of the granulate sublots in the fluid bed dryer.
    - Sieving of the granulate
4. Final blending of the three pooled sublots

Equipment:

- Stainless steel containers
- Stainless steel Vessel with agitator
- High Shear Mixing Granulator (Mixer / Chopper)
- Fluidized Bed Dryer
- Turbo Sieve
- Container Mixer (Mixer / Chopper)
- Sieving machine
- Powder suction conveyer
- Semi-automated packaging machine

(c) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Baton Rouge:

In process controls:

Parameter	**IPC**	**Acceptance criteria**
Yield	IPC 1	98 – 102 %
Loss on drying	IPC 2	≤ 1.2 %
Appearance	IPC 3	White, free flowing powder free from foreign matter
Filling weight	IPC 4	2020 g ± 1 % (2000 g – 2040 g)
Sealing integrity	IPC 5	Conforming

Vienna:

In process controls:

Parameter	**IPC**	**Acceptance criteria**
Yield	IPC 1	99 – 101 %
Loss on drying	IPC 2	≤ 0.8 %
Yield of final blend	IPC 3	95 – 101 %
Loss on drying	IPC 4	≤ 1.2 %
Filling weight	IPC - filling	2020 g ± 1 % (2000 g – 2040 g)
Sealing integrity	IPC - sealing	Conforming

Bulk holding time: 14 months (for both 300 and 600 kg)

6.4.3.4 Process validation *(NC, DSTS 268763, part 2.2.P.3.4.2)*

(a) Summary of the process validation protocol, and a summary of the completed process validation studies (if applicable):

Baton Rouge:

Section not affected by current change. To be completed in future submissions, when impacted by a change.

Vienna:

Validation Protocol # / Report #	Description	Status (Commitment / Completed)	Filed with Submission Control No.
Process validation protocol PVP_Aquaflor 50%_Rev01	Original process validation for site change from Bray (Ireland) to Vienna Batches (300 kg): A001, A002 and A003	Completed	NC, *DSTS 268763*
Process validation final report PV-FR_Aquaflor 50%_REV02			
Technical protocol TP-025-20 Rev01	Bulk holding time confirmation Batches (300 kg): A001, A002 and A003	Completed	
Technical report TR-025-20 Rev01			
Process assessment technical protocol TP-047-18, Rev01	Assessment for upscale to 600 kg Batch (600 kg): U136	Completed	
Process assessment technical report TR-047-18, Rev01			
Process validation protocol PV0060-01-P-01, Revision 01	Process validation for upscale to 600 kg Batches (600 kg): U137A01, U138A01 and U139A01	Completed	
Process validation report PV0060-01-FR-01, Revision 01			
Process validation protocol PV0064-02-P-01, Revision 01	Process verification for equivalency of alternative wet milling equipment Batch (600 kg): U153A	Completed	
Process validation report PV0064-02-FR-01, Revision 01			
Process validation protocol PV0089-02-P-01, Revision 01	Process verification for Apeloa florfenicol supplier Batches (600 kg): U168T	Completed	
Process validation report PV0089-02-FR-01, Revision 01			

Validation Protocol # / Report #	Description	Status (Commitment / Completed)	Filed with Submission Control No.
Technical protocol TP-066-20 Rev01	Bulk holding time confirmation Batches (600 kg): U168T (full container) and U167A (10 % full)	Completed	
Technical report VIE-07-081-TR version 01			
Process validation protocol PV0107-02-P-01 Revision: 01	Process verification for GMA 300 and Glatt fluid bed dryer refurbishment Batch (300 kg): 22A1001A (A174T)	Completed	
Process validation report PV0107-02-FR-01 Revision: 01			

6.4.4 Control of the drug product

6.4.4.1 Specification(s) *(NC, DSTS 194780, part 2.2.P.4.2; NC, DSTS 204657, parts 2.2.P.4.1 and 2.2.P.4.2)*

(a) Specification(s) for the drug product, including specification number and version, as well as test method number(s) and version(s) are required:

Baton Rouge:

Standard claimed (e.g., Professed, USP, BP, other)		Professed
Specification approved date		2020-10-30
Specification reference number and version		MS Aquaflor v01
Test	Acceptance Criteria (release and shelf-life)	Analytical Procedure (Type/Source/Version)
Appearance	White, free-flowing powder; free from foreign matter (R, S)	Visual / House / Delpharm: ATM 1100 v12, Baton Rouge and Neopharm: STM 096 effective 2004-07-30, Vienna: SPM-243E, Rev03
Water	≤ 3.5 % (R, S)	Karl Fischer / House / Delpharm: ATM 3474 v2.0, Baton Rouge and Neopharm: STM 059 effective 2017-08-23, Vienna: SPM-243E, Rev03
Identification of florfenicol by HPLC - RT	The retention time of the sample major peak is the same as that of the retention time of the standard peak. (R)	HPLC / House / Delpharm: ATM 3473 v02, Baton Rouge and Neopharm: STM 067 effective 2004-07-30 (refers to STM 097), Vienna: SPM-243E, Rev03
Assay of florfenicol by HPLC	450 to 550 mg/g (90.0 to 110.0 % of 500 mg/g) (R, S)	HPLC / House / Delpharm: ATM 3473 v02, Baton Rouge and Neopharm: STM 097 effective 2016-12-08, Vienna: SPM-243E Rev03
Related compounds by HPLC	Total: ≤ 2 % (S)	HPLC / House / Baton Rouge: STM 097 effective 2016-12-08 Vienna: SPM-243E, Rev03
Package integrity	No apparent changes observed (S)	Visual / House

(R) Release

(S) Shelf life

Vienna:

Standard claimed (e.g., Professed, USP, BP, other)		Professed
Specification approved date		2022-09-28
Specification reference number and version		SPM-243E, Rev03 (specification and methods)
Test	Acceptance Criteria (release and shelf-life)	Analytical Procedure (Type/Source/Version)
Appearance	White, free-flowing powder; free from foreign matter (R, S)	Visual / House
Water	≤ 3.5 % (R, S)	Karl Fischer / House
Identification of florfenicol by HPLC-RT	The chromatogram of the sample preparation obtained in the assay exhibits a peak at a retention time which corresponds to that exhibited by florfenicol peak in the standard solution chromatogram. The retention time ratio is 0.98 - 1.02. (R)	HPLC / House
Identification of florfenicol by HPLC-UV spectrum	For each injection, record the spectrum between 200 nm and 400 nm. The chromatogram of the sample preparation obtained in the assay exhibits a spectrum for florfenicol comparable to that exhibited by florfenicol in the response factor standard chromatogram. (R)	
Assay of florfenicol by HPLC	475 to 525 mg/g (R) 450 to 550 mg/g (S)	
Related compounds by HPLC	Individual: ≤ 0.5% Total: ≤ 1.5 % (S)	
Particle size	< 53 µm: ≤ 30 % > 600 µm: ≤ 5 % (R)	Sieve analysis / House
Package integrity	No apparent changes observed (S)	Visual / House

(R) Release

(S) Shelf life

6.4.5 Packaging

6.4.5.1 Description and specifications *(NC, DSTS 268763, parts 2.2.P.5.1 and 2.2.P.5.2)*

(a) Description of the primary and functional secondary packaging (e.g., foil pouches): Note: Indicate container closure system unit count or fill size and container size or volume, and for injectable products indicate the rubber closure formulation number.

Aquaflor is provided in individual 2 kg sealed laminated foil pouches.

Pouch Materials (outside to inside):

- Polypropylene - 25.4 µm
- LDPE - 25 .4 µm
- Aluminum - 8.9 µm
- Surlyn - 44.4 µm

Pouch specification: SPM-266DE REV 03

6.4.6 Stability

6.4.6.3 Post-approval Stability Protocol and Stability Commitment *(NC, DSTS 268763, part 2.2.P.6.3.2)*

(a) Stability protocol for production scale commitment batches (indicate protocol reference number and approval date):

Baton Rouge:

Stability protocol for initial process validation batches: SS013, approval date 2004-12-17

Protocol Parameter	Description
Storage conditions (including tolerances)	Long term: 25 ± 2°C / 60 ± 5 % RH Intermediate: 30 ± 2°C / 60 ± 5 % RH Accelerated: 40 ± 2°C / 75 ± 5 % RH
Testing frequency	Long term: 0 (initial), 3, 6, 9, 12, 18, 24, 36 and 48 months Intermediate: 0 (initial), 3, 6, 12, 24 and 36 months Accelerated: 0 (initial), 3 and 6 months
Number of batches per strength and batch sizes	Process validation batches 41017, 41106 and 41110
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

Stability protocol for Minsheng florfenicol: SS034, approval date 2011-11-30

Protocol Parameter	Description
Storage conditions (including tolerances)	Long term: 25 ± 2°C / 60 ± 5 % RH
Testing frequency	Long term: 0 (initial), 3, 6, 9, 12, 18, 24 and 36 months
Number of batches per strength and batch sizes	2 commercial scale batches
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

Vienna:

Formal stability protocol for upscale to 600 kg: GSP-AQF050_Upscale-PA-PV version 01, effective date 2018-10-30

Protocol Parameter	Description
Storage conditions (including tolerances)	Long term: 30 ± 2°C / 65 ± 5 % RH Accelerated: 40 ± 2°C / 75 ± 5 % RH
Testing frequency	Long term: 0 (initial), 1, 2, 3, 6, 9, 12, 18, 24 and 36 months Accelerated: 0 (initial), 1, 2, 3 and 6 months
Number of batches per strength and batch sizes	Process assessment batch U136 and Process validation batches U137A01, U138A01 and U139A01
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

Formal stability protocol for Bulk Hold Time: VIE-STA-FSP-AQF-001 version 02, approval date 2022-06-07

Protocol Parameter	Description
Storage conditions (including tolerances)	Long term: 30 ± 2°C / 65 ± 5 % RH
Testing frequency	Long term: 14 (initial after bulk hold storage), 24, 30 and 36 months
Number of batches per strength and batch sizes	BHT batch U167A
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

Formal stability protocol for Apeloa florfenicol: VIE-STA-FSP-AQF-002 version 02, approval date 2022-05-25

Protocol Parameter	Description
Storage conditions (including tolerances)	Long term: 30 ± 2°C / 65 ± 5 % RH Accelerated: 40 ± 2°C / 75 ± 5 % RH
Testing frequency	Long term: 0 (initial), 1, 2, 3, 6, 9, 12, 18, 24 and 36 months Accelerated: 0 (initial), 1, 2, 3 and 6 months
Number of batches per strength and batch sizes	Batches U168T, 22A1001A and 22A1002A
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

(b) Stability protocol for continuing batches (indicate protocol reference number and approval date):

Baton Rouge:

Stability protocol for ongoing stability: SS031, approval date 2010-12-22

Protocol Parameter	Description
Storage conditions (including tolerances)	30 ± 2°C / 65 ± 5 % RH
Testing frequency	0 (initial), 3, 6, 9, 12, 18, 24 and 36 months
Number of batches per strength and batch sizes	1 batch per year
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

Vienna:

Stability protocol for ongoing stability: VIE-STA-GSP-AQF-001 version 01

Protocol Parameter	Description
Storage conditions (including tolerances)	30 ± 2°C / 65 ± 5 % RH
Testing frequency	0 (initial), 12, 24, 30 and 36 months
Number of batches per strength and batch sizes	At the minimum one batch per year respectively 3 % of the produced batches, packed in the marketed container, have to be put on stability
Container closure system(s)	Refer to 6.4.5.1(a)
Tests and acceptance criteria	Refer to 6.4.4.1(a)
Other	-

6.6 Additional information for generic drug products

Not applicable

Pharmaceutical equivalence (*volume/page*):

Note to sponsor: Indicate the following information for the Canadian Reference Product (CRP) used in pharmaceutical equivalence studies.

Proprietary (brand) name of CRP	
DIN number	
Non-proprietary or common name of drug substance (active ingredient)	
Company name (manufacturer)	
Dosage form(s) and strength(s)	
Route of administration	