Date of Approval: November 14, 2024

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION (ANADA)

ANADA 200-803

PAQFLOR™

(florfenicol)

Type A medicated article to be used in the manufacture of Type C medicated feeds

Freshwater-reared salmonids, freshwater-reared finfish, catfish, and freshwater-reared warmwater finfish

Freshwater-reared salmonids: For the control of mortality due to furunculosis associated with *Aeromonas salmonicida*. For the control of mortality due to coldwater disease associated with *Flavobacterium psychrophilum*.

Freshwater-reared finfish: For the control of mortality due to columnaris disease associated with *Flavobacterium columnare*.

Catfish: For the control of mortality due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*.

Freshwater-reared warmwater finfish: For the control of mortality due to streptococcal septicemia associated with *Streptococcus iniae*.

Sponsored by:

Phibro Animal Health Corp.

Executive Summary

PAQFLOR™ (florfenicol) Type A medicated article to be used in the manufacture of Type C medicated feeds is approved for the following:

Freshwater-reared salmonids: For the control of mortality due to furunculosis associated with *Aeromonas salmonicida.* For the control of mortality due to coldwater disease associated with *Flavobacterium psychrophilum*.

Freshwater-reared finfish: For the control of mortality due to columnaris disease associated with *Flavobacterium columnare*.

Catfish: For the control of mortality due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*.

Freshwater-reared warmwater finfish: For the control of mortality due to streptococcal septicemia associated with *Streptococcus iniae.*

The reference listed new animal drug (RLNAD) is Aquaflor® (florfenicol) Type A medicated article, sponsored by Intervet, Inc., under New Animal Drug Application (NADA) 141-246. This is the first generic florfenicol Type A medicated article for use in freshwater-reared finfish.

Bioequivalence
The sponsor conducted two *in vivo* blood-level studies, one in Atlantic salmon and one in hybrid channel catfish, to show that the 500 g/kg PAQFLOR™ Type A medicated article is bioequivalent to the 500 g/kg Aquaflor® Type A medicated article. No serious adverse events were reported during the studies.

Human Food Safety
Under the NADA for Aquaflor®, the Food and Drug Administration (FDA) previously established the acceptable daily intake and tolerances for florfenicol residues, and these values also apply to PAQFLOR™.

The sponsor conducted one tissue residue study that supports assigning PAQFLOR™ the same withdrawal period that was previously established for Aquaflor®. Therefore, FDA has assigned a 15-day withdrawal period to PAQFLOR™ when it's fed as a Type C medicated feed to freshwater-reared salmonids, freshwater-reared finfish, catfish, and freshwater-reared warmwater finfish.

FDA determined that any residues of florfenicol in the edible tissues of treated fish are at a concentration that present a reasonable certainty of no harm to people when PAQFLOR™ is used according to the labeling.

User Safety
The labeling for PAQFLOR™ contains safety information for people who mix, handle, or administer the drug.

Conclusions
Based on the data submitted by the sponsor for the approval of PAQFLOR™, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-803

B. Sponsor

Phibro Animal Health Corp.
GlenPointe Centre East, 3d floor
300 Frank W. Burr Blvd., suite 21
Teaneck, NJ 07666

Drug Labeler Code: 066104

C. Proprietary Name

PAQFLOR™

D. Drug Product Established Name

florfenicol

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Type A medicated article to be used in the manufacture of Type C medicated feeds

G. Amount of Active Ingredient

500 g/kg (227.27 g/lb) florfenicol

H. How Supplied

2 kg packet

I. Dispensing Status

Veterinary feed directive (VFD)

J. Dosage Regimen

Freshwater-reared salmonids, freshwater-reared finfish, and catfish: 10-15 mg/kg body weight/day for 10 consecutive days.

Freshwater-reared warmwater finfish: 15 mg/kg body weight/day for 10 consecutive days.

K. Route of Administration

Oral

L. Species/Class

Freshwater-reared salmonids, freshwater-reared finfish, catfish, and freshwater-reared warmwater finfish

M. Indications

Freshwater-reared salmonids: For the control of mortality due to furunculosis associated with *Aeromonas salmonicida.* For the control of mortality due to coldwater disease associated with *Flavobacterium psychrophilum*.

Freshwater-reared finfish: For the control of mortality due to columnaris disease associated with *Flavobacterium columnare*.

Catfish: For the control of mortality due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*.

Freshwater-reared warmwater finfish: For the control of mortality due to streptococcal septicemia associated with *Streptococcus iniae.*

N. Reference Listed New Animal Drug

Aquaflor®; florfenicol; NADA 141-246; Intervet, Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD florfenicol 500 g/kg Type A medicated article. The *in vivo* blood-level studies were conducted in 273 Atlantic salmon and 311 healthy hybrid channel catfish. The pivotal parameters evaluated were the area under the composite concentration curve from time 0 to the last sampling timepoint ($AUC_{0\text{-}tlast}$) and from time 0 to the t_{max} ($AUC_{0\text{-}tmax}$), where t_{max} was defined as the sampling time when the maximum mean blood concentration from the composite curve of the RLNAD was observed. Bioequivalence was demonstrated between the 500 g/kg RLNAD florfenicol Type A medicated article and the 500 g/kg generic florfenicol Type A medicated article by the average bioequivalence approach as described in the Statistical Methods sections below. The study information is summarized below.

A. Blood-level Bioequivalence Study in Atlantic Salmon

Title: Pivotal Study to Determine the Bioequivalence of PAQFLOR™ Type A Medicated Article (florfenicol) to the Reference Labeled Product Aquaflor® Type A Medicated Article (florfenicol) when Administered in Medicated Feed to Atlantic Salmon (*Salmo salar* L.). (Study No. USD165-405)

Study Dates: December 17, 2021, to February 28, 2023

Study Locations:

In-life phase: Prince Edward Island, Canada

Bioanalytical testing: East Lothian, Scotland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 500 g/kg florfenicol Type A medicated article and the RLNAD 500 g/kg Aquaflor® (florfenicol) Type A medicated article in fasted Atlantic salmon.

Study Animals: Two hundred and seventy-three Atlantic salmon (220 intended for blood sampling and 53 as spares) weighing between 120 and 170 g on study day -7.

Experimental Design: A randomized, masked, single period, two-treatment, single-dose parallel study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies and Organization for Economic Cooperation and Development Principles of Good Laboratory Practice.

Drug Administration: Two hundred and eight animals received 10 mg/kg of either the generic or RLNAD florfenicol based on randomization.

Measurements and Observations: The plasma concentrations of florfenicol were measured using a validated bioanalytical method. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked, two-treatment, single- dose, parallel study using a destructive sampling design with 104 fish in each treatment group and 12 fish sampled for the pre-dose blood sampling time.

Each fish to be included in a treatment group was arbitrarily netted from a pre-treatment holding tank and administered either the test article or RLNAD once via oral gavage. After treatment administration, each fish was placed into an individual study tank; study tanks were randomly assigned to treatment groups and sampling timepoints prior to treatment administration. Each fish in the treatment groups received only one treatment (test article or RLNAD) and was sampled for blood collection at a single timepoint only.

Blood samples were collected from 12 fish per treatment group at each of the 6 early timepoints and were collected from 8 fish per treatment group at 4 late timepoints. Also, blood samples were collected from an additional 12 fish that were not assigned to either treatment group, and these blood samples served as the pre-treatment (time 0) samples for both treatment groups. Given the destructive sampling incurred during blood collection in which each fish provided only one blood sample, composite pharmacokinetic (PK) parameters were calculated. The mean plasma concentration and standard deviation were calculated for each combination of time point and treatment group. The primary endpoints were the area under the concentration curve from time 0 to the last observation ($AUC_{0\text{-}tlast}$) and to the t_{max} ($AUC_{0\text{-}tmax}$), where t_{max} was defined as the timepoint associated with the maximum mean blood concentration of the RLNAD. Both AUCs were calculated using the linear trapezoidal rule: $\Sigma_i(t_i - t_{i-1}) * (C_i + C_{i-1})/2$, where C_i was the mean concentration at time t_i.

The 90% confidence interval (CI) of the ratio (generic/RLNAD) for each primary endpoint was calculated using Fieller's method. The variance of each primary endpoint was estimated using the method of Bailer (J. Pharm and Biopharm, 1988).

Results:

As seen in the table below, bioequivalence is established because the 90% confidence interval of the ratio of both composite $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}tmax}$ are contained within the acceptance limits of 0.80 to 1.25 (Table II.1).

Table II.1. Bioequivalence Evaluation

Parameter	Generic	RLNAD	Ratio◊	Lower 90% CI	Upper 90% CI
Composite $AUC_{0\text{-}tlast}$ (h*ng/mL)	118049†	115937†	1.02	0.98	1.06
Composite $AUC_{0\text{-}tmax}$ (h*ng/mL)	31994†	31478†	1.02	0.95	1.08
T_{MAX} (hours)	12	12	NE	NE	NE

† Composite AUC calculated using mean concentration at each timepoint
◊ Ratio = Generic/RLNAD
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 500 g/kg PAQFLOR™ (florfenicol) Type A medicated article and the RLNAD 500 g/kg Aquaflor® (florfenicol) Type A medicated article are bioequivalent in Atlantic salmon.

B. Blood-level Bioequivalence Study in Hybrid Channel Catfish

Title: Pivotal Study to Determine the PK Bioequivalence of Florfenicol Administered in Medicated Feed Containing Either Aquaflor® or PAQFLOR™ in Hybrid Channel Catfish

(*Ictalurus punctatus* ♀ x *I. furcatus* ♂). (Study No. USD165-521)

Study Dates: December 17, 2021, to September 25, 2023

Study Locations:

In-life phase: Prince Edward Island, Canada

Bioanalytical testing: East Lothian, Scotland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood level bioequivalence data for the generic 500 g/kg PAQFLOR™ (florfenicol) Type A medicated article and the RLNAD 500 g/kg Aquaflor® (florfenicol) Type A medicated article in fasted hybrid channel catfish.

Study Animals: Three hundred and eleven hybrid channel catfish (190 intended for blood sampling and 121 as spares) weighing between 70 and 317 g at enrollment.

Experimental Design: A randomized, masked, single period, two-treatment, single-dose parallel study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies and Organization for Economic Cooperation and Development Principles (OECD) of Good Laboratory Practice.

Drug Administration: One hundred and eighty animals received 15 mg/kg of either the generic or RLNAD florfenicol based on randomization.

Measurements and Observations: The plasma concentrations of florfenicol were measured using a validated bioanalytical method. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked, two-treatment, single- dose, parallel study using a destructive sampling design with 90 fish in each treatment group and 10 additional fish for pre-dose sampling. Appropriate randomization of animal to treatment and tank/sampling timepoint was performed.

Given the destructive sampling incurred during blood collection in which each fish provided only one blood sample, composite pharmacokinetic (PK) parameters were calculated. The mean plasma concentration and standard deviation were calculated for each combination of time point and treatment group. The primary endpoints evaluated were the area under the composite concentration curve from time 0 to the last sampling timepoint ($AUC_{0\text{-}tlast}$) and to the t_{max} ($AUC_{0\text{-}tmax}$), where t_{max} was defined as the sampling time when the maximum mean blood concentration from the composite curve of the RLNAD was observed; t_{max} was 10 hours in this study. Both AUCs were calculated using the linear trapezoidal rule: $\Sigma_i(t_i - t_{i-1}) * (C_i + C_{i-1})/2$, where C_i was the mean concentration at time t_i.

The upper and lower bounds of the 90% confidence interval (CI) on the ratio (generic/RLNAD) for each primary endpoint was calculated using Fieller's method. The

variance of each primary endpoint was estimated using the method of Bailer (J. Pharm and Biopharm, 1988). Bioequivalence is established because the estimated upper and lower bounds of the 90% confidence interval for the ratios (generic/RLNAD) are contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below, composite $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-tmax}}$ fall within the prescribed bounds (Table II.2). The values of T_{MAX} obtained (from the composite concentration curves) for the generic article and RLNAD were presented.

Table II.2. Bioequivalence Evaluation

Parameter	Generic	RLNAD	Ratio◊	Lower 90% CI	Upper 90% CI
Composite $AUC_{0\text{-tlast}}$ (h*ng/mL)	189879†	188642†	1.01	0.92	1.10
Composite $AUC_{0\text{-tmax}}$# (h*ng/mL)	50647†	48092†	1.05	0.91	1.21
T_{MAX} (hours)	9	10	NE	NE	NE

† Composite AUC calculated using mean concentration at each timepoint
◊ Ratio = Generic/RLNAD
#t_{max} was defined as the sampling time when the maximum mean blood concentration from the composite curve of the RLNAD was observed; it was 10 hours in this study.
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 500 g/kg PAQFLOR™ (florfenicol) Type A medicated article and the RLNAD 500 g/kg Aquaflor® (florfenicol) Type A medicated article are bioequivalent in hybrid channel catfish.

III. HUMAN FOOD SAFETY

A. Acceptable Daily Intake and Tolerances for Residues

The acceptable daily intake (ADI) for total residue of florfenicol is 10 µg/kg of body weight per day. The tolerances established for the RLNAD apply to the generic product. A tolerance of 1 parts per million (ppm) is established for florfenicol amine (the marker residue) in muscle (the target tissue) of catfish, and 1 ppm in muscle/skin (the target tissue) of freshwater-reared warmwater finfish (other than catfish) and salmonids, under 21 CFR 556.283.

B. Withdrawal Period

Title: Comparative Single Time Point Study with the Pioneer Product, Aquaflor, and the Generic Product, PAQFLOR™, in Rainbow Trout (*Oncorhynchus mykiss*) at the Label Withdrawal Period. (Test Facility Study Number QCATC244, Sponsor Study Number USD165-426)

Study Dates: May 14, 2021, to June 10, 2022

Study Locations:

In-life phase: Prince Edward Island, Canada

Bioanalytical testing: Edinburgh, United Kingdom

Study Design:

The study was conducted in compliance with OECD Principles of Good Laboratory Practice, 21 CFR Part 58 Good Laboratory Practice Standards for Nonclinical Laboratory Studies, and applicable Standard Operating Procedures.

Test Article: The test article was florfenicol Type A medicated article. The RLNAD was Aquaflor® (florfenicol) Type A medicated article. Type C medicated feed was prepared by top-coating the test and reference articles onto commercial EWOS Vita 4 mm pellet feed at an inclusion rate of 1.25 g florfenicol/kg feed to deliver 15 mg florfenicol/kg body weight/day at a feeding rate of 1.2% body weight/day.

Study Animals: Forty rainbow trout (*Oncorhynchus mykiss*) were used. Mean fish weights at Study Day -8 were 406.8 g (range 367 to 438 g) for fish receiving the test article and 411.4 g (range 375 to 462 g) for fish receiving the RLNAD. Fish were housed in a flow-through system consisting of two 1500 L tanks. The temperature of the water flowing through the system was maintained at 12 ± 2ºC.

Dosing: There were two treatment groups, with each group contained 20 rainbow trout. One group received Type C medicated feed top-coated with the test article and one group received Type C medicated feed top-coated with the RLNAD. The inclusion rate was 1.25 g florfenicol/kg of feed with a feeding rate of 1.2% body weight/day, delivering a dose of 15 mg florfenicol/kg body weight/day. The dosing period was 10 days.

Sampling: After 15 days withdrawal, 15 fish were randomly selected from each tank, and muscle with adhering skin was collected from each fish.

Tissue Analysis: Tissue samples were analyzed using the official method entitled Determination of “Florfenicol Amine Residues in Aquaculture Species by HPLC with UV Detection (v. 2.0)”.

Results:

Concentrations of florfenicol amine in all samples from both treatment groups were below the limit of quantitation (0.219 ppm).

Conclusion:

The tissue residues resulting from fish fed the test article or the RLNAD cannot be compared because the concentrations of florfenicol amine were below the limit of quantitation (LOQ) in both groups. However, the tissue samples were analyzed with the official method that was validated around the tolerance, and the LOQ of the method (0.219 ppm) is substantially less than the tolerance (1 ppm). Therefore, there is no human food safety concern that can be identified with the test article under the same conditions of use as the RLNAD. Thus, the data support assigning florfenicol Type A medicated article the withdrawal period assigned to the RLNAD: 15 days.

C. Analytical Method for Residues

The validated analytical method for analysis of residues of florfenicol is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PAQFLOR™:

WARNING: Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling PAQFLOR™ (florfenicol) should use protective clothing, gloves, goggles and NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Safety Data Sheet (SDS) contains more detailed occupational safety information.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that PAQFLOR™, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

Additionally, data demonstrate that residues in food products derived from freshwater-reared salmonids, freshwater-reared finfish, catfish, and freshwater-reared warmwater finfish treated with PAQFLOR™ will not represent a public health concern when the product is used according to the label.