

AQUACULTURE DRUG APPROVAL DEVELOPMENT STATUS

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH): RESEARCH AND DEVELOPMENT PLAN AND LABEL CLAIM MATRICES FOR SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA) APPROVALS

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DEVELOPED UNDER THE FEDERAL-STATE AQUACULTURE DRUG APPROVAL PARTNERSHIP PROJECT, A PROJECT OF THE ASSOCIATION OF FISH AND WILDLIFE AGENCIES

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**OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)
(Version 1, November 2007)**

ABBREVIATIONS, ACRONYMS, & CONTACT INFORMATION FOR ENTITIES IN TABLE

AADAP	Aquatic Animal Drug Approval Partnership Program—Dr. David Erdahl, U.S. Fish and Wildlife Service, 4050 Bridger Canyon Road, Bozeman, Montana 59715; Phone: 406-994-9904; Fax: 406-582-0242; E-mail: Dave_Erdahl@fws.gov
AOI	All Other Information Technical Section, not included in any of the other sections, that is pertinent to an evaluation of effectiveness or safety [21 CFR § 514.1(b)(8)(iv)]
CVM	Aquaculture Drugs Team (HFV-131), Division of Therapeutic Drugs for Food Animals, Office of New Animal Drug Evaluations, Center for Veterinary Medicine, U.S. Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855; Dr. Donald Prater; Phone: 301-827-7567; E-mail: DPrater@CVM.FDA.GOV
Efficacy	Effectiveness Technical Section includes pivotal & supportive studies that show whether or not a drug is effective for its intended use [21 CFR § 514.1(b)(8)(i)]
FOI	Final Freedom of Information summary generated by CVM based on draft FOIs developed by researchers for each study [21 CFR § 514.11(e)(2)(ii)]
INAD	Investigational New Animal Drug exemption [21 CFR 511]
Label	Labeling Technical Section includes labeling and package inserts [21 CFR § 514.1(b)(3)]
NADA	New Animal Drug Application [21 CFR 514]
NADA Coordinator	Rosalie (Roz) Schnick, National Coordinator for Aquaculture New Animal Drug Applications, Michigan State University, 3039 Edgewater Lane, La Crosse, Wisconsin 54603-1088; Phone: 608-781-2205; Fax: 608-783-3507; E-mail: RozSchnick@centurytel.net
PHIBRO	Sponsor of oxytetracycline dihydrate (Terramycin® 200 for Fish): Paul F. Duquette, Director, Global Regulatory Affairs, Phibro Animal Health, 65 Challenger Road, 3 rd floor, Ridgefield Park, NJ 07660; Phone: 201-329-7375; E-mail: paul.duquette@pahc.com ;
Product Chemistry	Product Chemistry Technical Section includes chemistry, manufacturing, and controls [21 CFR § 514.1(b)(4-6)]
PMF	Public Master File can contain safety and efficacy data and information generated with public funds (Guidance Document #57)
Toxicology	Part of Human Food Safety Technical Section, toxicological testing includes genetic toxicity tests and mammalian safety studies (e.g., acute, subchronic) (Guidance Document #3)
UAZ	University of Arizona; Rodney Williams, Department of Veterinary Sciences, Tucson, AZ 85721; Phone: 602-293-3502; Fax: 602-293-3502; E-mail: rodneyw@Ag.arizona.edu
UMESC	Upper Midwest Environmental Sciences Center—Dr. William Gingerich, 2630 Fanta Reed Road, La Crosse, Wisconsin 54603; Phone: 608-783-6451; Fax: 608-783-6066; E-mail: bill_gingerich@usgs.gov

KEY TO COLOR CODING

COLOR	STATUS
	No current plans and/or funds
	In progress or planned; funded
	Submitted to CVM
	Accepted by CVM

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)

Oxytetracycline dihydrate (Terramycin® for Fish) NADA approvals (9/23/70, 6/30/06)

ORIGINAL NADA APPROVAL FOR MONO-ALKYL TRIMETHYL AMMONIUM OXYTETRACYCLINE (TERRAMYCIN® FOR FISH) (9/23/70)

Species/Class: Salmonids, catfish, and lobsters

Indications:

Salmonids: Control of ulcer disease caused by *Hemophilus piscium*, furunculosis caused by *Aeromonas salmonicida*, bacterial hemorrhagic septicemia caused by *Aeromonas liquifaciens*, and pseudomonas disease

Catfish: For the control of bacterial hemorrhagic septicemia caused by *Aeromonas liquifaciens* and pseudomonas disease in catfish

Lobsters: Control of Gaffkemia caused by *Aerococcus viridans*

Recommended Dosage:

Salmonids and catfish: 2.5 to 3.75 g of oxytetracycline per 100 lb of fish for 10 consecutive days

Lobsters: 1 g oxytetracycline/lb of medicated feed administered as the sole ration for 5 consecutive days

Species/Class: Pacific salmon

Indications: For marking of skeletal tissue

Recommended Dosage: 250 mg of oxytetracycline per kg of fish per day in fish feed

SUPPLEMENTAL NADA APPROVAL FOR OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN 200® FOR FISH) (6/30/06)

This supplement provides for the change of the active ingredient from the mono-alkyl (C8-C18) trimethylammonium oxytetracycline to the oxytetracycline dihydrate, the change of the oxytetracycline concentration from 100 g/lb to 200 g/lb, the change of the product name to reflect the change in the oxytetracycline concentration, and the addition of the approved lobster indication to the label for the control of Gaffkemia caused by *Aerococcus viridans*.

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)

Status of Technical Sections that support all supplemental NADA approvals

Technical Section	Entity—Data—Action	Impediments or Cost—Action
Product Chemistry (quaternary ammonium salt)	PHIBRO (INAD #11-368)—Product chemistry package/ quaternary ammonium salt—previously accepted	None
Product Chemistry (dihydrate salt)	PHIBRO (INAD #11-368)—Product chemistry package/change quaternary ammonium salt to dihydrate salt—accepted 6/30/06	None—Technical Section is complete
Environmental Safety (pond, flow-through, & recirculating systems)	PHIBRO (INAD #11-368) & others—Environmental assessment—previously accepted	None
Environmental Safety (pond, flow-through, & recirculating systems/all finfish)	UMESC (INAD #11-366 & PMF #5646)—Environmental assessment/all finfish—revision submitted 4/13/07 & additions submitted 8/7/07	None—pending acceptance
Human Food Safety—Toxicology	PHIBRO (INAD #11-368) & others—Toxicology—previously accepted	None
Human Food Safety—Residue Chemistry (salmonids & catfish)	PHIBRO (INAD #11-368) & others—Residue depletion studies in salmonids and catfish—previously accepted	None
Human Food Safety—Residue Chemistry (rainbow trout)	UMESC (INAD #11-366 & PMF #5646)—Bridged official microbial inhibition assay with HPLC method/rainbow trout—accepted 9/11/97	None
Human Food Safety—Residue Chemistry (all finfish)	UMESC (INAD #11-366 & PMF #5646)—Liquid chromatographic determination/six fish species fillets—accepted 12/8/00 & follow-up response 9/9/02	None
Human Food Safety—Residue Chemistry (all finfish)	UMESC (INAD #11-366 & PMF #5646)—Bridged official microbial inhibition assay with robust HPLC method/all finfish—accepted 12/8/00 & follow-up response 9/9/02; final acceptance 10/27/04	None
Human Food Safety—Residue Chemistry (all freshwater-reared salmonids)	UMESC (INAD #11-366 & PMF #5646)—Marker residue depletion studies for all juvenile freshwater-reared salmonids below 9° C—accepted 9/9/99	None
Human Food Safety—Residue Chemistry (all salmonids)	UMESC (INAD #11-366 & PMF #5646)—Extrapolated withdrawal times for all sizes of salmonids—accepted 5/17/02	None
Human Food Safety—Microbiological toxicology of residues (all finfish)	PHIBRO (INAD #11-368), UMESC, & NADA Coordinator—Microbiological toxicology of residues—Guideline # 159/all finfish—accepted 9/20/06	None
Human Food Safety—Microbial Food Safety (freshwater-reared salmonids)	AADAP (INAD #9332)—Microbial food safety—Guideline #152/freshwater-reared salmonids—Hazard Characterization—Accepted 3/15/07	None
Human Food Safety (Technical Section Complete Letter)	PHIBRO (INAD #11-368)—Human Food Safety/Technical Section Complete Letter request—submitted 7/2/07	None
Target Animal Safety (catfish and salmonids)	PHIBRO (INAD #11-368) & others—Target animal safety/salmonids and catfish—previously accepted	None
Target Animal Safety (all freshwater-reared finfish)	UMESC (INAD #11-366 & PMF #5646)—Target animal safety/all freshwater-reared finfish—accepted 12/19/03	None—Technical Section is complete
Efficacy (all label claims/all finfish)	UMESC (INAD #11-366 & PMF #5646)—Developed analytical method to detect oxytetracycline in feed in support of all INAD testing—accepted 7/29/98	None

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)

LABEL CLAIM #1

SPECIES: FRESHWATER-REARED SALMONIDS

INDICATIONS: For the control of mortality in freshwater-reared salmonids due to systemic coldwater disease associated with *Flavobacterium psychrophilum*

DIRECTIONS FOR USE: Apply Terramycin® 200 for Fish in medicated feed at a dose of 3.75 grams oxytetracycline per 100 pounds of fish per day for ten consecutive days.

LABEL CLAIM #2

SPECIES: *ONCORHYNCHUS MYKISS*

INDICATIONS: For the control of mortality in *Oncorhynchus mykiss* due to systemic columnaris disease associated with *Flavobacterium columnare* (*Flexibacter columnaris*)

DIRECTIONS FOR USE: Apply Terramycin® 200 for Fish in medicated feed at a dose of 3.75 grams oxytetracycline per 100 pounds of fish per day for ten consecutive days.

LABEL CLAIM #3

SPECIES: SALMONIDS

INDICATIONS: For skeletal marking of salmonids

DIRECTIONS FOR USE: Apply Terramycin® 200 for Fish in medicated feed at a dose of 11.35 grams oxytetracycline per 100 pounds of fish (250 mg per kg of fish) per day for four consecutive days.

Technical Section	Entity—Data—Action	Impediments or Cost—Action
Efficacy (systemic coldwater disease/salmonids)	UMESC (INAD #11-366 & PMF #5646)—Efficacy/systemic coldwater disease/all freshwater-reared salmonids—accepted Data Call-in as supportive 2/1/00	None
Efficacy (systemic coldwater disease/salmonids)	AADAP (INAD #9006 & 9332)—Efficacy/coldwater disease/all freshwater-reared salmonids—accepted as pivotal 11/23/01	None—Technical Section is complete
Efficacy (systemic columnaris disease/salmonids)	UMESC (INAD #11-366 & PMF #5646)—Efficacy/systemic columnaris disease/all freshwater-reared salmonids—accepted Data Call-in as supporting 2/1/00	None
Efficacy (systemic columnaris disease/steelhead trout)	AADAP (INAD #9006 & 9332)—Efficacy/systemic columnaris disease/steelhead trout—accepted as pivotal 11/14/00	None—Technical Section is complete
Efficacy (skeletal marking/salmonids)	AADAP (INAD #9006 & 9332)—Efficacy/skeletal marking/salmonids —submitted 2007	None—pending acceptance
Label	PHIBRO (INAD #11-368) & NADA Coordinator—Label/systemic coldwater disease/salmonids, systemic columnaris disease/ <i>Oncorhynchus mykiss</i> , & skeletal marking/salmonids—submitted 7/23/07	None—pending acceptance
FOI	CVM—FOI/systemic coldwater disease/salmonids, systemic columnaris disease/ <i>Oncorhynchus mykiss</i> , & skeletal marking/salmonids—in progress with PHIBRO, UMESC, & AADAP input	None—pending acceptance
AOI	PHIBRO (INAD #11-368) & NADA Coordinator—AOI/systemic coldwater disease/salmonids, systemic columnaris disease/ <i>Oncorhynchus mykiss</i> , & skeletal marking/salmonids—planned before supplemental NADA submission	None—pending acceptance
NADA Package	PHIBRO (INAD #11-368) & NADA Coordinator—NADA package/systemic coldwater disease/salmonids, systemic columnaris disease/ <i>Oncorhynchus mykiss</i> , & skeletal marking/salmonids—in progress	None—pending acceptance

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)

LABEL CLAIM #4

SPECIES: FRESHWATER-REARED FINFISH

INDICATIONS: For the control of mortality in freshwater-reared finfish due to systemic columnaris disease associated with *Flavobacterium columnare* (*Flexibacter columnaris*)

DIRECTIONS FOR USE: Apply Terramycin® 200 for Fish in medicated feed at a dose of 3.75 grams oxytetracycline per 100 pounds of fish per day for ten consecutive days.

Technical Section	Entity—Data—Action	Impediments or Cost—Action
Efficacy (systemic columnaris disease/salmonids)	UMESC (INAD #11-366 & PMF #5646)—Efficacy/systemic columnaris disease/all freshwater-reared salmonids—accepted Data Call-in as supporting 2/1/00	None
Efficacy (systemic columnaris disease/steelhead trout)	AADAP (INAD #9006 & 9332)—Efficacy/systemic columnaris disease/steelhead trout—accepted as pivotal 11/14/00	None
Efficacy (systemic columnaris disease/salmonids)	AADAP (INAD #9006 & 9332)—Efficacy/systemic columnaris disease/Coho salmon or Chinook salmon—planned	None—pending acceptance
Efficacy (systemic columnaris disease/coolwater & warmwater fish)	No entity identified—Pivotal efficacy/systemic columnaris disease/coolwater & warmwater fish—not planned	Needs to be planned
Label	PHIBRO (INAD #11-368) & NADA Coordinator—Label/systemic columnaris disease/freshwater-reared finfish—i planned if efficacy accepted	None—pending acceptance
FOI	CVM—FOI/systemic columnaris disease/freshwater-reared finfish—planned if efficacy accepted	None—pending acceptance
AOI	PHIBRO (INAD #11-368) & NADA Coordinator—AOI/systemic columnaris disease/freshwater-reared finfish—planned if efficacy accepted	None—pending acceptance
NADA Package	PHIBRO (INAD #11-368) & NADA Coordinator—NADA package/systemic columnaris disease/freshwater-reared finfish—planned if efficacy accepted	None—pending acceptance

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)

LABEL CLAIM #5

SPECIES: COOLWATER AND WARMWATER FINFISH

INDICATIONS: For the control of mortality in coolwater and warmwater finfish due to motile aeromonad septicemia associated with *Aeromonas hydrophila*

DIRECTIONS FOR USE: Apply Terramycin® 200 for Fish in medicated feed at a dose of 3.75 grams oxytetracycline per 100 pounds of fish per day for ten consecutive days.

Technical Section	Entity—Data—Action	Impediments or Cost—Action
Efficacy (bacterial hemorrhagic septicemia/catfish and salmonids)	PHIBRO (INAD #11-368) & others—Efficacy/bacterial hemorrhagic septicemia/salmonids and catfish—previously accepted	None
Efficacy (<i>Aeromonas</i> sp./northern pike)	UMESC (PMF #5646)—Efficacy/ <i>Aeromonas</i> sp./northern pike—accepted Data Call-in as supportive 2/1/00	None
Efficacy (motile aeromonad septicemia/coolwater and warmwater finfish)	UMESC & PHIBRO—Pivotal efficacy/motile aeromonad septicemia/coolwater and warmwater finfish—being planned with NCRAC funds	None—pending acceptance
Label	PHIBRO (INAD #11-368) & NADA Coordinator—Label/motile aeromonad septicemia/coolwater and warmwater finfish—planned when efficacy accepted	None—pending acceptance
FOI	CVM—FOI/motile aeromonad septicemia/coolwater and warmwater finfish—planned when efficacy accepted	None—pending acceptance
AOI	PHIBRO (INAD #11-368) & NADA Coordinator—AOI/motile aeromonad septicemia/coolwater and warmwater finfish—planned when efficacy accepted	None—pending acceptance
NADA Package	PHIBRO (INAD #11-368) & NADA Coordinator—NADA package/motile aeromonad septicemia/coolwater and warmwater finfish—planned when efficacy accepted	None—pending acceptance

OXYTETRACYCLINE DIHYDRATE (TERRAMYCIN® 200 FOR FISH)

LABEL CLAIM #6

SPECIES: PENAEID SHRIMP

INDICATIONS: For the control of mortality in penaeid shrimp due to necrotizing hepatopancreatitis

DIRECTIONS FOR USE: Apply Terramycin® 200 for Fish in medicated feed at a dose of 1.5 to 4.5 grams oxytetracycline per kilograms of feed per day for 14 consecutive days.

Technical Section	Entity—Data—Action	Impediments or Cost—Action
Environmental Safety (pond, flow-through, & recirculating systems/penaeid shrimp)	UAZ (INAD #8069)—Environmental assessment additional data/penaeid shrimp—in progress	None—pending acceptance
Human Food Safety—Toxicology (penaeid shrimp)	PHIBRO (INAD #11-368)—Mammalian toxicology—needs to provide proprietary data to derive ADI for penaeid shrimp	None—pending acceptance
Human Food Safety—Residue Chemistry (penaeid shrimp)	UAZ (INAD #8069)—Residue Chemistry/penaeid shrimp—accepted 11/4/99	None
Human Food Safety—Microbiological toxicology of residues (penaeid shrimp)	PHIBRO (INAD #11-368) & UAZ—Microbiological toxicology of residues—Guideline # 159/penaeid shrimp—Paper argument to add to other NADAs (8-804 & 95-143) for aquaculture NADAs—accepted 8/15/06	None
Human Food Safety—Microbial Food Safety (penaeid shrimp)	PHIBRO (INAD #11-368) & UAZ—Microbial food safety—Guideline #152/ freshwater-reared salmonids—Qualitative Risk Assessment—in progress	None—pending acceptance
Target Animal Safety (penaeid shrimp)	UAZ (INAD #8069)—Target animal safety/penaeid shrimp—submitted 8/04; CVM responded by requesting more data	None—pending acceptance
Efficacy (necrotizing hepatopancreatitis/penaeid shrimp)	UAZ (INAD #8069)—Efficacy/necrotizing hepatopancreatitis/penaeid shrimp—accepted 6/28/00	None
Label	PHIBRO (INAD #11-368) & NADA Coordinator—Label/necrotizing hepatopancreatitis/penaeid shrimp—planned	None—pending acceptance
FOI	CVM—FOI/necrotizing hepatopancreatitis/penaeid shrimp—planned with PHIBRO & UAZ input	None—pending acceptance
AOI	PHIBRO (INAD #11-368) & NADA Coordinator—AOI/necrotizing hepatopancreatitis/penaeid shrimp—planned	None—pending acceptance
NADA Package	PHIBRO (INAD #11-368) & NADA Coordinator—NADA package/necrotizing hepatopancreatitis/ penaeid shrimp—planned	None—pending acceptance