

Guidance for Industry

Status of Clove Oil and Eugenol for Anesthesia of Fish

This level 2 guidance document provides information regarding the use of clove oil and its components for the anesthesia of fish.

Comments and suggestions regarding this guidance document should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. All comments should be identified with the exact title of the document.

For questions regarding information about the drug approval process and INAD files, contact Dr. Joan Gotthardt, Center for Veterinary Medicine (HFV-130), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7571.

For questions regarding information about regulatory discretion, contact Ms. Fran Pell, Center for Veterinary Medicine (HFV-235), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-0188.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
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This document represents the Agency's current thinking on the status of clove oil and eugenol for anesthesia of fish. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used as long as it satisfies the requirements of the applicable statute and regulations.

The Food and Drug Administration's Center for Veterinary Medicine (FDA/CVM) has had many inquiries regarding the use of clove oil, and/or the active components of clove oil, as an anesthetic for use in fish. This CVM Guidance Document provides information regarding the use of clove oil and its components for the anesthesia of fish.

1. Clove Oil vs. Eugenol

Clove oil is actually a mixture of different compounds. The three significant active ingredients are eugenol, isoeugenol and methyleugenol. 'Clove oil' is 85 to 95% eugenol. Isoeugenol and methyleugenol make up 5 to 15% of the remaining ingredients. Isoeugenol is the compound considered by some aquaculturists to have the best anesthetic effect. However, neither clove oil nor any individual active ingredient of clove oil (eugenol, isoeugenol, or methyleugenol) is approved for use for the anesthesia of fish.

2. Approval Status

Clove oil has been affirmed as Generally Recognized as Safe (GRAS) as a substance added directly to human food (21 CFR 184.1257).

Eugenol is GRAS in animal feed (21 CFR 582.60) and isoeugenol is cleared for use in human food (21 CFR 172.515). Both compounds are listed as synthetic flavoring substances and adjuvants.

Eugenol (not clove oil) is used as a component in dental cement for temporary fillings (21 CFR 872.3275). It is considered a device exempt from premarket notification procedures.

The fact that clove oil or its components are GRAS for use in dental cement or as food additives under these conditions does not justify the use of these products as new animal drugs.

Neither clove oil nor eugenol is approved as a new animal drug to treat or mitigate any diseases in any species in the U.S. Therefore, the use of either clove oil or eugenol as an anesthetic for fish makes them unapproved new animal drugs.

3. Anesthetic Choices for Use in Fish

MS-222 (Finquel[®] or Tricaine-S[®]), also known as Tricaine methanesulfonate are approved new animal drugs that can be used as an anesthetic in fish. The conditions of use for this drug can be viewed at

<http://dil.vetmed.vt.edu/AdvancedNADA/NadaPrint.cfm?NadaString=042-427> and <http://dil.vetmed.vt.edu/AdvancedNADA/NadaPrint.cfm?NadaString=200-226>.

In addition, carbon dioxide gas may be used as an anesthetic for cold-, cool-, and warm water fish and sodium bicarbonate may be used as an anesthetic on all fish (the sodium bicarbonate is principally an alternate source of carbon dioxide). The use of carbon dioxide gas and sodium bicarbonate as anesthetics makes these compounds new animal drugs. At this time, however, the Agency has chosen not to take regulatory action for the above use of these compounds. Details about the uses of these two compounds can be found at (<http://www.fda.gov/cvm/index/aquaculture/LRPDrugs.pdf>).

4. Human Food Safety

Clove oil and isoeugenol have been used in foods and eugenol has been used in animal feeds. Concern for this class of chemical compounds led to the nomination of eugenol, isoeugenol, and methyleugenol for investigation under the National Toxicology Program (NTP). The NTP conducts studies in nominated drugs and chemicals to determine their potential to produce cancer. Studies have been completed for eugenol and methyleugenol, and are planned for isoeugenol. NTP determined that eugenol is an equivocal carcinogen and methyleugenol is carcinogenic to rodents. The contamination of clove oil with methyleugenol or isoeugenol raises the level of concern for human safety.

You can see the status of toxicology studies conducted on these compounds by going to the NTP website at <http://ntp-server.niehs.nih.gov/>. Once there, use the search function. A search for 'eugenol' brings up all the related test results.

5. Investigational New Animal Drug (INAD) Exemption Files

For many new animal drugs, INAD files are established for the purpose of studying the drug to gather data to support FDA approval for a particular claim. Most of these files belong to pharmaceutical companies and are proprietary to protect trade secrets. FDA/CVM cannot even acknowledge the existence of such files. Other INADs are held by public entities such as the US Fish and Wildlife Service (USFWS). These files are often disclosable and may involve other groups in the data collection process. Under specific conditions an investigator has use of the investigational drug prior to its approval.

At this time, there is one publicly-disclosable INAD exemption file for the use of isoeugenol as a fish anesthetic. This is held by the USFWS under the supervision of Dave Erdahl. The product has been given an investigational withdrawal time of 21 days for the dosing regimen being used in the current studies. If you are

conducting studies that could be cited to help demonstrate the safety or effectiveness of isoeugenol in fish, you may contact Dr. Dave Erdahl to discuss working under the USFWS INAD. He can be reached by email at dave_erdahl@fws.gov.

6. Use of Investigational Drugs in a Laboratory Setting

The Code of Federal Regulations (CFR) allows use of investigational drugs in a laboratory setting without specific notification to CVM (21 CFR 511.1(a)). However, these uses are intended for preliminary studies to support the approval of the drug, not for routine clinical use on laboratory animals for another purpose.

There is also a provision in the CFR for use of drugs in animals in teaching settings, etc. at 21 CFR 201.125. You can access the full citations through the Government Printing Office (GPO) access website at <http://www.gpo.gov/nara/cfr/index.html>.

Eugenol may not be used in any form on animals (fish) that could possibly be consumed by humans, even if the treatment occurs in a laboratory setting. This includes endangered species, or species that otherwise may be released into public waters where they would be available for human consumption. The only exception would be under the auspices of an INAD exemption in which a treatment authorization, including an appropriate investigational withdrawal time, has been obtained from FDA/CVM.

7. Contacts

For further information, you can contact:

Dr. Joan Gotthardt - (301) 827-7571 - for information about the drug approval process and INAD files.

Ms. Fran Pell - (301) 827-0188 - for information about regulatory discretion.