Date: September 17, 2025:

FREEDOM OF INFORMATION SUMMARY

Import Tolerance

VMF 006-394

ampicillin hydrate

Perciformes fish

50 parts per billion (ppb) ampicillin in muscle with adhering skin

Petitioner:

ALVIS INC

Table of Contents

I. GENERAL INFORMATION

A. File Number

VMF 006-394

B. Petitioner

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Tokyo, Japan 160-0007

U.S. Agent Name and Address:

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Exponent
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C. Drug Established Name

ampicillin hydrate

D. Pharmacological Category

Antimicrobial

E. Species/Class

Perciformes fish

F. Import Tolerances for Drug Residues in Edible Tissues

50 ppb ampicillin in muscle with adhering skin

II. HUMAN FOOD SAFETY

A. Toxicology

1. JECFA Toxicological Monograph

The toxicological evaluation of ampicillin was performed at the 85th meeting of the Joint Food Agricultural Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) in 2017. The toxicological report was published in the WHO Technical Report Series 1008 of the 85th report of the JECFA (2018), and toxicological monograph was published in the WHO Food Additive Series 76 (2020).

To evaluate the toxicity of ampicillin in the human diet, JECFA considered data on the pharmacokinetics (including metabolism), acute toxicity, short-term and long-term toxicity, genotoxicity, carcinogenicity, microbiological effects and

observations in humans. The series of toxicology studies included were summarized in Table II.1.

Table II.1. Summary of Toxicology Studies

Study Type	Description
Acute/Subacute Oral Toxicity Studies in Rodents	The oral lethal median dose (LD_{50}) in mice and rats was greater than 10 g/kg body weight (bw). 14-day oral (gavage) toxicity in study in mice. A NOEL/NOAEL* of 1600 mg/kg bw/day was established.
Subchronic Oral Toxicity Study in Mice	3-month oral (gavage) toxicity study in mice. A NOEL/NOAEL larger than 2140 mg/kg bw/day (the highest dose) was identified.
Subchronic Oral Toxicity Studies in Rats	3-month oral (gavage) toxicity study in rats. A NOEL/NOAEL of 1070 mg/kg bw/day was identified based on body weight decreases and diarrhea observed at the next higher dose.
Chronic Oral Toxicity Studies in Mice	103-week oral (gavage) toxicity study in mice. A LOEL/LOAEL** was established at 1070 mg/kg bw/day as increased salivation and decreased activity, increased incidences of forestomach lesions, hyperplasia of bone marrow and mandibular lymph nodes were found at all treatments.
Chronic Oral Toxicity Studies in Rats	2-year oral (gavage) toxicity study in rats. A LOEL/LOAEL of 536 mg/kg bw/day was established due to diarrhea, excessive urination, and chromodacryorrhea observed at all treatments.
Genetic Toxicology Studies	Overall evidence from results of *in vivo* and *in vitro* genotoxicity studies suggest that ampicillin has no genotoxic potential.

*(NOEL/NOAEL): no-observed-effect level/ no-observed-adverse-effect level
**(LOEL/LOAEL): lowest-observed-effect level/ lowest-observed-adverse effect level

2. Toxicology Assessment

The Agency evaluated the toxicological and microbiological (i.e., effects on human intestinal flora) effects of ampicillin residues based on publicly available information including the JECFA toxicological monograph. The evaluation of effects on human intestinal flora included the assessment of two endpoints of concern, *i.e.*, disruption of the colonization barrier and increase in the population of resistant bacteria.

The agency concluded that the import tolerance of 50 ppb, equivalent to 15 µg for a 60 kg person consuming 0.3 kg muscle per day or 0.25 µg/kg bw/day, provides a substantial margin of safety. This level is significantly below the lowest LOEL/LOAEL of 536 mg/kg bw/day identified in the available toxicology studies. It also offers a wide margin relative to the JECFA established ADI of 3 µg/kg bw/day

based on microbiological endpoint. Furthermore, it is below the allergenicity threshold of 30 µg/day, equivalent to 0.5 µg/kg bw/day, which is established for benzylpenicillin, a compound with a higher allergenic potential than ampicillin. Overall, the Agency concludes that the import tolerance of 50 ppb for ampicillin residues in muscle with adhering skin is sufficiently low and is unlikely to pose any toxicological or microbiological concerns to human health.

B. Residue Chemistry

1. Summary of Residue Chemistry Studies

   To evaluate the disposition and depletion of ampicillin hydrate residues in the edible tissue of Perciformes fish, the Agency considered study summaries and information from the JECFA residue monograph. A residue chemistry evaluation of ampicillin in fish was performed at the 85th meeting of the JECFA (FAO 21[1]; 2018). The JECFA concluded that parent ampicillin is the relevant marker residue and recommended a Maximum Residue Limit (MRL) of 50 ppb in finfish muscle and muscle plus skin in natural proportions. In 2018, the 41st Session of the Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Program adopted the 50-ppb MRL recommended by JECFA (CAC 41, 2018[2]). The Agency concludes that an import tolerance of 50 ppb is appropriate for U.S. consumers.

2. Target Tissue and Marker Residue

   The target tissue is muscle with adhering skin. The marker residue is parent drug, ampicillin.

3. Import Tolerance

   An import tolerance of 50 ppb is established for ampicillin in the muscle with adhering skin of Perciformes fish.

4. Withdrawal Period

   A withdrawal period is not assigned when establishing an import tolerance.

C. Analytical Method for Residues

1. Description of the Analytical Method

   The Food and Drug Administration monitors for ampicillin residues in fish muscle using the multi-residue monitoring procedure described in Laboratory Information Bulletin (LIB) # 4653A.

[1] https://openknowledge.fao.org/bitstreams/ac5c0b4f-f127-489e-904f-285f66c58749/download
[2] https://www.fao.org/fao-who-codexalimentarius/sh-proxy/it/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-701-41%252FReport%252FFINAL%252FREP18_CACe.pdf

2. Availability of the Analytical Method

   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.

III. AGENCY CONCLUSIONS

The Center for Veterinary Medicine assigns an import tolerance of 50 ppb for ampicillin in Perciformes fish. The data submitted in support of establishment of an import tolerance for ampicillin hydrate in Perciformes fish satisfy the requirements of section 512(a)(6) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 510, Subpart C.