CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 9 (a) **CX/RVDF 12/20/11 Add. 1**

April 2012

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twentieth Session

San Juan, Puerto Rico, 7-11 May 2012

DRAFT PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION BY JECFA

Replies of Kenya and United States of America to CL 2010/50-RVDF

KENYA

Issues and observations

i. Participation by developing countries in the development of the document has been poor (Out of the nine drugs on the draft priority list, none was sponsored by any African country)

ii. The proposed priority list of veterinary drugs is acceptable

Comments

i. Developing countries should be active participants and work in a more coordinated manner as well as generate data that would enable them propose veterinary drugs to be included in priority list

UNITED STATES OF AMERICA

(i) LASALOCID

Administrative Information

1. Member submitting the request for inclusion

   United States

2. Veterinary Drug Names

   Lasalocid

3. Trade Names

   Avatec

4. Chemical Names

   CAS No 25999-20-6

5. Names and addresses of basic producers

   Pfizer Animal Health
   7000 Portage Road
   Kalamazoo, MI 49001-0199

Purpose, Scope and Rationale

6. Identification of the food safety issue (residue hazard)

   Residues in edible tissues

7. Assessment against the criteria for the inclusion on the priority list

   - A member has proposed the compound for evaluation (USA)

   - A member has established good veterinary practices with regard to the compound (but distinct regional differences exist which must be recognized)

   - The compound has the potential to cause public health and/or international trade problems

   - The compound is available as a commercial product (registered globally)

   - There is a commitment that a dossier will be made available (Pfizer)

Risk Profile Elements

8. Justification for use

   Control of coccidiosis in poultry

9. Veterinary use pattern

   Medicated feed additive

10. Commodities for which Codex MRLs are required

    All Poultry (chickens, turkeys, ducks, quail, pheasants) tissues and eggs

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework

    Full toxicology and residue data are available (albeit some data are old)

12. Specific request to risk assessors

The specific requests to JECFA from CCRVDF are:

- Establish an ADI and MRLs for lasalocid in poultry tissues

- Take into account residue pharmacokinetics and differences in regional residue data when recommending MRLs that accommodate international uses of lasalocid.

Background

Lasalocid has been reviewed by the FDA/CVM, CVMP and EFSA.

The CVMP assigned MRLs for lasalocid in poultry but at the time of the submission the muscle MRL was established at the limit of quantitation of the assay at 20 µg/kg. This value is currently serving as the standard for management of international trade, especially in Asia.

Subsequent residue studies using more sensitive methods have discovered that the alpha depletion phase of lasalocid is very rapid but a prolonged beta phase results in a very slow depletion of the remaining residues. This slow phase hovers around 10-20 µg/kg and since the slope at this point is nearly flat, it is possible for residues in a single bird to assay above the MRL, causing a violation. Relative to both the CVMP and the EFSA ADI values, these findings would not be considered unsafe, but would still be in violation. These depletion characteristics of lasalocid continue to cause international trade problems in Asia and could potentially cause issues for poultry exports into the European Union.

Consequently, CCRVDF requests that JECFA consider the following when recommending MRLs for lasalocid:

- Take into account the pattern of use which encompasses a 0-day withdrawal period in the USA and Australia and the withdrawal period in the EU and Asia of 5 days.) and the resulting residues in edible tissues.

- Consistent with paragraph 34 of Section IV: Risk Analysis of the Procedural Manual, seek to recommend MRLs that are no more trade-restrictive than necessary,

Available information

13. Countries where the veterinary drug is registered

Globally.

14. National/Regional MRLs or any other applicable tolerances

CVMP MRLs (5-day withdrawal, EFSA recommended)

Muscle: 20 µg/kg
Liver: 100 µg/kg
Kidney: 50 µg/kg
Skin/Fat: 100 µg/kg
Eggs: 150 µg/kg

JAPAN MRLs (currently under review; default limits assigned; 7-day withdrawal (all feed additives are subject to this WDP):

Muscle: 10 µg/kg
Liver: 10 µg/kg
Kidney: 10 µg/kg
Skin/Fat: 10 µg/kg
Eggs: 10 µg/kg

USATolerances (0-day withdrawal):

Muscle: Not established
Liver: 400 µg/kg
Kidney: Not established
Skin/Fat: 1200 µg/kg

AUSTRALIAN MRLs (0-day withdrawal):

Muscle: 50 µg/kg
Liver: 700 µg/kg
Kidney: 700 µg/kg
Skin/Fat: 1200 µg/kg
Eggs: 50 µg/kg

15. List of data (pharmacological, toxicological, metabolism, residue depletion, analytical methods) available

Complete standard toxicology package and residue package including a validated analytical method.

Timetable

16. Date when data could be submitted to JECFA

Within two months following a call for data. Studies and data are available but would need to be compiled into a dossier. Target date would be for a dossier to be ready for the next JECFA meeting in 2013, to provide recommendations for the 21st CCRVDF.

17. The prospect of completing the work within a reasonable period of time

No new studies are contemplated and the pharmaceutical sponsor is confident it can complete a dossier by the time indicated.

(ii) PHENYLPYRAZOLE

Administrative Information

1. Member submitting the request for inclusion

   United States

2. Veterinary Drug Names

   PF-00241851

3. Trade Names

   Not established

4. Chemical Names

   5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2-difluoro-1-(trifluoromethyl)cyclopropyl]-1H-pyrazole-3-carbonitrile

   Chemical Class: phenyl pyrazole

   CAS Number: 856225-89-3

5. Names and addresses of basic producers

   Pfizer Animal Health
   7000 Portage Road
   Kalamazoo, MI 49001-0199

Purpose, Scope and Rationale

6. Identification of the food safety issue (residue hazard)

   Residues in edible tissues

7. Assessment against the criteria for the inclusion on the priority list

   Per CX/RVDF 12/20/8 (January 2012), Item 13:

   - A member has proposed the compound for evaluation (USA)

   - The compound has the potential to cause public health and/or international trade problems

   - There is a commitment that such commercial availability is pending (Pfizer)

   - There is a commitment that a dossier will be made available (Pfizer)

Risk Profile Elements

8. Justification for use

   PF-0241851 is a potent insect GABA-gated chloride channel agonist. This action blocks pre- and post-synaptic transfer of chloride ions across cell membranes, resulting in lethal uncontrolled activity of the central nervous system of insects and acari on livestock.

9. Veterinary use pattern

   Subcutaneous injection

10. Commodities for which Codex MRLs are required

    Beef cattle liver, kidney, muscle and fat

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework

    Full toxicology and residue data will be available

12. Specific request to risk assessors

- Elaborate ADI and MRLs for PF-00241851

- Once the ADI is determined, establish MRLs (consistent with ADI) that maximally promote international trade (i.e. full utilization of the ADI)

Available information

13. Countries where the veterinary drug is registered

None at this time. Dossiers to be filed in Brazil, the European Union and the United States in summer 2013.

14. National/Regional MRLs or any other applicable tolerances

None at this time. Current Sponsor plans include application for MRLs and/or import tolerances in Brazil, the European Union and the United States in summer 2013.

15. List of data (pharmacological, toxicological, metabolism, residue depletion, analytical methods) available

Complete standard toxicology package and residue package including a validated analytical method

Timetable

16. Date when data could be submitted to JECFA

July 2013

17. The prospect of completing the work within a reasonable period of time

Sponsor is confident it can complete a dossier by the time indicated.

(iii) ZILPATEROL HYDROCHLORIDE

Administrative information

1. Member submitting the request for inclusion:

United States of America

2. Veterinary Drug Name:

Zilpaterol hydrochloride (INN)

3. Trade Name:

Zilmax®

4. Chemical Names:

IUPAC name: (±)-Trans-4,5,6,7-Tetrahydro-7-hydroxy-6-(isopropylamino) imidazo[4,5,1-jk]-[1]benzazepin -2(1H)- one, monohydrochloride,

CAS name: Trans(±)-4,5,6,7-Tetrahydro-7-hydroxy-6-[(1-methyl-ethyl)amino]-imidazo[4,5,1-jk] [1]benzazepin-2(1H)-one, monohydrochloride

5. Names and addresses of basic producers:

MSD Animal Health, Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer, The Netherlands

Purpose, Scope and Rationale

6. Identification of the food safety issue:

Residue hazard

7. Assessment against the criteria for the inclusion on the priority list:

   All five criteria for inclusion of the compound on the priority list are met.

   - The compound is proposed by the United States of America for evaluation

   - The compound has been marketed and is used for many years in various markets (refer to para 8)

   - Meat and meat products derived from animals treated with the product are globally traded and there is potentially a residue hazard and trade issues

   - The compound is commercially available in all markets where it is registered (refer to para 8)

   - MSD Animal Health commits to make the dossier available

Risk profile elements

8. Justification for use:

   The product is indicated for increased rate of body weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement for slaughter at the end of the feeding period

9. Veterinary use pattern:

   The product is mixed into the feed of the animals

10. Commodities for which Codex MRLs are required:

    Muscle, liver and kidney

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework:

    JECFA has evaluated similar compounds (beta-agonist) in the past and should be familiar with this class of compounds. In addition, a comprehensive data package is available which should facilitate the evaluation of the compound

12. Specific request to risk assessors:

    None

Available information1

13. Countries where the veterinary drugs is registered:

    Canada, Colombia, Costa Rica, Dominican Republic, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, South Africa, United States of America

14. National/Regional MRLs or any other applicable tolerances:

    Tolerances (USA, Mexico) and MRLs have been established but vary between countries. Tolerances in the US and Mexico are 12 ppb for liver and 10 ppb for muscle. Muscle MRLs have been set between 1-2 ppb and MRLs for liver, kidney and fat have been commonly set at 30 ppb, 20 ppb and 20 ppb respectively.

15. List of data available:

    - Pharmacology/ Safety pharmacology studies (general and special pharmacological studies)

    - Pharmacokinetics and metabolism studies in laboratory animals (rat, micro-swine)

    - Acute toxicology studies (mice, rat, rabbits, guinea pig; various routes)

    - Sub-chronic toxicity studies (rat, dog, micro-swine and monkey)

    - Chronic toxicology study (rat)

    - Reproductive toxicology study (rat)

    - Embryotoxicity/teratogenicity studies (rat, mice and rabbit)

- Genotoxicity with zilpaterol HCL (various in vivo and in vitro)
- Genotoxicity with metabolite (various in vivo and in vitro)
- Carcinogenicity studies (mice, rat)
- Observation in humans (four studies)
- Metabolism and residue depletion studies in the target animal (cattle)
- Validated residue method

Timetable

16. Date when data could be submitted to JECFA:

The dossier can be provided (electronically and/or paper) within a lead time of 4-6 weeks