

# CODEX ALIMENTARIUS COMMISSION



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization

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Agenda Item 9

CRD22

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**  
**CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS**  
**Twenty-third Session**  
**Houston, Texas, United States of America, 17 – 21 October 2016**  
**PRIORITY LIST NOMINATION**  
**Submitted by New Zealand**

## Administrative Information

1. Member submitting the request for inclusion

New Zealand

2. Veterinary Drug Names

Bismuth subnitrate (BSN); bismuth hydroxide nitrate oxide, basic bismuth nitrate and bismuth nitrate.

3. Trade Names

Teat-Seal; Orbeseal

4. Chemical Names

Chemical Class: Teat Sealant

5. CHEMICAL FORMULA

$4\text{Bi}(\text{NO}_3)(\text{OH})_2 \cdot \text{BiO}(\text{OH})$  (European Pharmacopoeia - Ph. Eur.) OR

$\text{Bi}_5\text{O}(\text{OH})_9(\text{NO}_3)_4$

6. CHEMICAL STRUCTURE

BSN has a 3 dimensional structure that consist of two basic units.

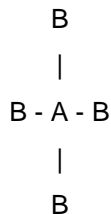
Unit A is  $\text{BiO}(\text{OH})$

This is sometimes drawn as  $\text{O}=\text{Bi}-\text{OH}$

Unit B is  $\text{BiNO}_3(\text{OH})_2$

This is Bi surrounded by three subunits: one  $-\text{NO}_3$  and two  $-\text{OH}$

Four unit B structures are arrayed around one unit A structure:



$4\text{Bi}(\text{NO}_3)(\text{OH})_2 \cdot \text{BiO}(\text{OH})$  (European Pharmacopoeia - Ph. Eur.) OR

$\text{Bi}_5\text{O}(\text{OH})_9(\text{NO}_3)_4$

7. CAS Number: for BSN is 1304-85-4.

8. Names and addresses of basic producers

Zoetis

333 Portage Road

Kalamazoo, MI 49007

**Purpose, Scope and Rationale**

## 9. Identification of the food safety issue (residue hazard)

Bismuth residues in milk (implications for safety and international trade)

## 10. 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 (NZ)
- The compound has the potential to cause public health and/or international trade problems
- The material is commercially available in a large number of global markets
- There is a commitment that a dossier will be made available (Zoetis)

**Risk Profile Elements**

## 11. Justification for use

BSN is a component in Orbeseal® an implantable medical device placed in cow teats to prevent mastitis by providing a physical (i.e., non-pharmacological) barrier to entry of potential pathogens into the teats and udder during non-milk producing periods (i.e., the “dry” period). The Orbeseal teat seal is infused into the teats with a 4-gram, single use, intramammary infusion tube. Orbeseal consists of 65.0% BSN in a base material of 29.4% liquid paraffin (e.g., mineral oil) as a vehicle, 4.8% aluminum tristearate as a thickening agent and 0.8% colloidal anhydrous silica as a stabilizer. BSN is used in the Orbeseal device to increase the viscosity and density of the implanted material so as to prevent the components in the device from migrating from the teats into the udder.

During the “freshening” period, following onset of milk production, Orbeseal is removed manually from the teats by expressing the milk. However, a residual amount of BSN contained in Orbeseal remains in the udder. Low but quantifiable concentrations of bismuth that are greater than background levels have been found in milk from cows treated with Orbeseal.

## 12. Veterinary use pattern

Intramammary Administration (multiple approved labels are available)

## 13. Commodities for which Codex MRLs are required

Bovine milk

**Risk assessment needs and questions for the risk assessors**

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

Full MRL package as submitted to CVMP for assessment. Additional residue depletion studies in milk. Assessment report by USA consultant group to establish that BSN was approved for GRAS listing in that market.

## 15. Specific request to risk assessors

- Elaborate ADI for BSN, if necessary.
- Once the ADI is determined (if necessary ), establish MRLs, if necessary, that maximally promote international trade (i.e. full utilization of the ADI)

**Available information**

## 16. Countries where the veterinary drug is registered

A large number of markets, globally, including the USA, EU, NZ, AUS and Korea.

## 17. National/Regional MRLs or any other applicable tolerances

Orbeseal has been considered to be a device by the Food and Drug Administration (FDA) in the U.S. and such medical products are not specifically regulated by the FDA. In the EU, where veterinary medical products used in food animals are regulated differently than in the U.S. (EMEA 1997), the Committee for Veterinary Medicinal Products reviewed the safety data on BSN and approved the use of Orbeseal for intramammary use in cows (EMEA 1999). The committee concluded that there was no need to establish a maximum residue level (MRL) for its inclusion in Annex II to Council Regulation (EEC) number 2377/90 (EMEA 1999).

The Expert Panel, in the USA, having independently and collectively, critically evaluated the data and information summarized above, concludes that bismuth subnitrate, meeting appropriate European Pharmacopeia specifications and produced and used consistent with current Good Manufacturing Practice (cGMP) is safe for its intended use as a component of Orbeseal®. The Expert Panel also concludes that other experts qualified by scientific training and experience, and evaluating the same data and information, would generally conclude that bismuth subnitrate is safe for use as a component of Orbeseal®. The Expert Panel further concludes that bismuth subnitrate is Generally Recognized as Safe (GRAS) based on scientific procedures, supported by a history of safe use, for use as a component of Orbeseal®. It is their opinion that other qualified and competent scientists reviewing the same publicly available data would reach the same scientific conclusion. Therefore, BSN is safe, and is GRAS at the resulting bismuth residue levels found in bovine milk from use of the Orbeseal device. Because BSN is GRAS, residues of bismuth in milk and milk products are GRAS from its approved use as a component in the Orbeseal device used for cows. BSN is, therefore, excluded from the definition of a food additive, and may be used in the U.S. without the promulgation of a food additive regulation by the FDA under 21 CFR.

### Bismuth Residue Requirements in Export Markets

Country	MRL	Comment
New Zealand	Default of 0.1 mg/kg***	Milk WHP 96 hours (8 milkings)
Australia	Not required, use permitted*	Milk WHP 96 hours (8 milkings)
EU	Not required, use permitted**	No milk or preslaughter withdrawal.
Japan	Default value = 0.01 mg/kg	Default value set as compound has not been formally assessed.
USA	Not required. Considered as a "device" not a veterinary medicinal product.	No milk or pre-slaughter withdrawal.
Korea	Not required, use permitted	Milk WHP 96 hours

\* Table 5 of MRL Standard 2012

\*\*Annex II of Council Regulation (EEC) No 2377/90 (Appendix 1).

\*\*\* Proposal to make it an exception from MRLs (2016).

18. List of data (pharmacological, toxicological, metabolism, residue depletion, analytical methods) available  
Complete standard toxicology package and residue package including a validated analytical method (for Bismuth)

Berstad A, Olafsson S, Tefera S, Berstad K, Hundal O, Bergseth M, and Wilhelmsen I. 1996. Bismuth therapy for *Helicobacter pylori* infection. A review of five years experience at a university hospital in Norway. *J Physiol Pharmacol.* 47:31-49.

Bierer DW. 1990. Bismuth subsalicylate: history, chemistry, and safety. *Rev Infect Dis.* 12:S3-S8.

Briggs GG, Freeman RK, and Yaffe SJ. 1994. *Drugs in Pregnancy and Lactation.* In: A reference guide to fetal and neonatal risk, 95. 4th ed. Baltimore, MD: Williams and Wilkins.

Boudéne C, Bouley G, Belegaud J. 1979. Recherches Étiologiques et Pathogéniques expérimentales sur la toxicité du sous-nitrate de bismuth lourd micronisé chez le rat [In French]. *J Pharmacol (Paris).* 10, 2:105-117.

Buge A, Supino-Viterbo V, Rancurel G, and Pontes C. 1981. Epileptic phenomena in bismuth toxic encephalopathy. *J Neurol Neurosurg Psychiatry.* 44:62-67.

Carr-Locke D and Wicks AB. 1986. A double-blind, endoscopically assessed evaluation of a bismuth subnitrate preparation (Roter®) and cimetidine in the treatment of duodenal ulcer. *Br J Clin Pract.* 40:373-375.

Cava-Montesinos P, Cervera ML, Pastor A, and de la Guardia M. 2003. Determination of ultratrace bismuth in milk samples by atomic fluorescence spectrometry. *J AOAC Int.* 86:815-822.

Chaleil D, Lefevre F, Allain P, and Martin GJ. 1981. Enhanced bismuth digestive absorption in rats by some sulfhydryl compounds: NMR study of complexes formed. *J Inorg Biochem.* 15:213-221.

Cook AJ and Friday JE. 2005. Pyramid Servings Intakes in the United States 1999-2002, 1 day. <http://www.ba.ars.usda.gov/cnrg>.

- California State University (CSU). 2005. Selected rules for solubility. <http://www.csudh.edu/oliver/chemdata/data-ksp.htm>.
- Cross Vetpharm Group Limited (CVGL). 1999. Concentration of bismuth in bovine milk following intramammary administration of teat seal at the recommended dose. Study No. 9814.
- Demirbas A. 2001. Concentrations of 21 metals in 18 species of mushrooms growing in the East Black Sea region. *Food Chem.* 75:453-457.
- Divrikli U, Saracoglu S, Soylak M, and Elci L. 2003. Determination of trace heavy metal contents of green vegetable samples from Kayseri-Turkey by flame atomic absorption spectrometry. *Fresenius Environ Bull.* 12:1123-1125.
- Dresow B, Fischer R, Gabbe EE, Wendel J and Heinrich HC. 1992. Bismuth absorption from <sup>205</sup>Bi-labelled pharmaceutical bismuth compounds used in the treatment of peptic ulcer disease. *Scand J Gastroenterol.* 27:333-336
- European Agency for the Evaluation of Medicinal Products (EMA). 1997. Committee for Veterinary Medicinal Products. Bismuth Subnitrate, Bismuth Subcarbonate, Bismuth Subgallate, Bismuth Subsalicylate: Summary Report 1. EMA/MRL/201/97-FINAL. April 1997. <http://www.emea.eu.int/pdfs/vet/mrls/020197en.pdf>.
- European Agency for the Evaluation of Medicinal Products (EMA). 1999. Committee for Veterinary Medicinal Products. Bismuth Subnitrate. Extension to intramammary administration. Summary Report 2. EMA/MRL/705/99-FINAL. October 1999. <http://www.emea.eu.int/pdfs/vet/mrls/070599en.pdf>.
- Food and Drug Administration (FDA). 2003. Labeling for oral and rectal over-the-counter drug products containing aspirin and non-aspirin salicylates; Reye's syndrome warning. Final rule. *Fed Reg.* Apr 17 68(74):18861-9.
- Food and Drug Administration (FDA). 2005. Guidance for industry: General principles for evaluating the safety of compounds used in food-producing animals. <http://www.fda.gov/cvm/Documents/GFI003.pdf>.
- Gillain G and Rutagengwa J. 1985. Determination of Zn, Cd, Pb, Cu, Sb and Bi in milk. *Analisis.* 13:471-473.
- Gold LS, Stone TH, Manley NB, Garfinkel GB, and Ames BN. 2005. Carcinogenic Potency Project Bismuth oxychloride (CAS #7787-59-9): Rats and mice cancer test summary. <http://potency.berkeley.edu/>.
- Gosselin RE, Hodge HC, Smith RP, and Gleason MN. 1984. *Clinical toxicology of commercial products.* 5th ed. Baltimore, MD: Williams and Wilkins. Location 218, Section II-134.
- Gunderson V, Bechmann IV, Behrens A, and Sturup S. 2000. Comparative investigation of concentrations of major and trace elements in organic and conventional Danish agricultural crops. 1. Onions (*Allium cepa* Hysam) and peas (*Pisum sativum* Ping Pong). *J Agric Food Chem.* 48:6094-6102.
- Hall RJ and Farber T. 1972. Determination of bismuth in body tissues and fluids after administration of controlled doses. *J Assoc Anal Chem.* 55:639-642.
- Hamilton EI and Minski MJ. 1972. Abundance of the chemical elements in man's diet and possible relations with environmental factors. *Sci Total Environ.* 1:375-394.
- Hillemand P, Palliere M, Laquais B, and Bouvet P. 1977. Bismuth treatment and blood bismuth levels [In French]. *Sem Hop.* 53:1663-1669.
- Hundal O, Bergseth M, Gharehnia B, Andersen KJ, and Berstad A. 1999. Absorption of bismuth from two bismuth compounds before and after healing of peptic ulcers. *Hepatogastroenterology.* 46:2882-2886.
- Hursh JB and Brown C. 1969. Tissue distribution of <sup>212</sup>Bi in rats. *Proc Soc Exp Biol Med.* 131:116-120.
- Jung MC, Thornton I, and Chon HT. 2002. Arsenic, Sb and Bi contamination of soils, plants, waters and sediments in the vicinity of the Dalsung Cu-W mine in Korea. *Sci Total Environ.* 295:81-89. <http://venus.semyung.ac.kr/~jmc65/home/profile/work/stoten1.pdf>
- Jungreis AC and Schaumburg HH. 1993. Encephalopathy from abuse of bismuth subsalicylate (Pepto-Bismol). *Neurology.* 43:1265-1267.
- Lambert JR. 1991. Pharmacology of bismuth-containing compounds. *Rev Infect Dis.* 13:S691-S695.
- Lechat P and Kisch R. 1986. [Bismuth encephalopathy: a reappraisal of risk factors] 4. *Gastroenterol Clin Biol.* 10:562-569.

- Lechat P, Morel-Maroger L, Cluzan R, Flouvat F, and Fontagne J. 1968. Experimental study of the effects of the prolonged ingestion of bismuth subnitrate combined with other substances [In French]. *Therapie*. 23:445-457.
- Levitt MD, Springfield J, Furne J, Koenig T, and Suarez FL. 2002. Physiology of sulfide in the rat colon: use of bismuth to assess colonic sulfide production. *J Appl Physiol*. 92:1655-1660.
- Lione A. 1987. Nonprescription drugs as a source of aluminum, bismuth, and iodine during pregnancy. *Reprod Toxicol*. 1:243-252.
- Menge H, Gregor M, Brosius B, Hopert R, and Lang A. 1992. Pharmacology of bismuth. *Eur J Gastroent Hepatol*. 4:S41-S47.
- Momen AA, Zachariadis GA, Anthemidis AN, and Stratis JA. 2005. Development and validation of routine analysis methods for the determination of essential, nonessential, and toxic minor and trace elements in cereal and cereal flour samples by inductively coupled plasma-atomic emission spectrometry. *Journal of AOAC International*. 88:1797-1810.
- Noach LA, Eekhof JL, Bour LJ, Posthumus Meyjes FE, Tytgat GN, and Ongerboer de Visser BW. 1995. Bismuth salts and neurotoxicity. A randomised, single-blind and controlled study. *Hum Exp Toxicol*. 14:349-355.
- United States National Toxicology Program. (NTP). 1982. Salmonella study summary on bismuth subsalicylate CAS #14882-18-9. NTP Study I.D. 731380. [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm).
- Pamphlett R, Stoltenberg M, Rungby J, and Danscher G. 2000. Uptake of bismuth in motor neurons of mice after single oral doses of bismuth compounds. *Neurotoxicol Teratol*. 22:559-563.
- Parisis NE and van den Heede MA. 1992. Antimony uptake and correlation with other metals in mushroom species. *Toxicol Environ Chem*. 36:205-216.
- Preussmann R and Ivankovic S. 1975. Absence of carcinogenic activity in BD rats after oral administration of high doses of bismuth oxychloride. *Food Cosmet Toxicol*. 13:543-544.
- Seefeldt KE and Weimer BC. 2000. Diversity of sulfur compound production in lactic acid bacteria. *J Dairy Sci*. 83:2740-2746.
- Serfontein WJ and Mekel R. 1979. Bismuth toxicity in man II. Review of bismuth blood and urine levels in patients after administration of therapeutic bismuth formulations in relation to the problem of bismuth toxicity in man. *Res Commun Chem Pathol Pharmacol*. 26:391-411.
- Slikkerveer A, de Wolff, FA. 1989. Pharmacokinetics and toxicology of bismuth compounds. *Med. Toxicol. Adverse Drug Exp*. 4. 5: 303-323.
- Slikkerveer A, Helmich RB, Van der Voet GB, De Wolff FA. 1995. Absorption of bismuth from several bismuth compounds during in vivo perfusion of rat small intestine. *J Pharmaceu. Sci*. 84:512-514.
- Terre Haute Laboratories. 2002. Evaluate the safety and product compatibility of Orbeseal® during the dry period and early lactation when used in conjunction with commercially available intramammary dry cow antibiotics. Pfizer: Veterinary Research and Development. Experiment #1431E-60-02-375.
- Tillman LA, Drake FM, Dixon JS, and Wood JR. 1996. Review article: safety of bismuth in the treatment of gastrointestinal diseases. *Aliment Pharmacol Ther*. 10:459-467.
- United States Department of Agriculture (USDA). 2002. TAP Reviews: Bismuth Subsalicylate. <http://www.ams.usda.gov/nop/NationalList/TAPReviews/BismuthSubsalicylate.pdf>
- United States Department of Agriculture (USDA). 2005. National Nutrient Database for Standard Reference, Release 18. <http://www.nal.usda.gov/fnic/foodcomp/Data/>.
- United States National Toxicology Program. (NTP). 1982. Salmonella study summary on bismuth subsalicylate CAS #14882-18-9. NTP Study I.D. 731380. [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm).
- VICALIN. 2005. Product Information. [www.halychpharm.com.ua/products/d7\\_2\\_eng.html](http://www.halychpharm.com.ua/products/d7_2_eng.html).
- Whitehead MW, Phillips RH, Sieniawska CE, Delves HT, Seed PT, Thompson RP, and Powell JJ. 2000. Double-blind comparison of absorbable colloidal bismuth subcitrate and nonabsorbable bismuth subnitrate in the eradication of *Helicobacter pylori* and the relief of nonulcer dyspepsia. *Helicobacter*. 5:169-175.
- Winship KA. 1983. Toxicity of bismuth salts. *Adv Drug React Ac Pois Rev*. 2:103-121.

Wuilloud RG, Kannamkumarath S, and Caruso JA. 2004. Multielemental speciation analysis of fungi Porcini (*Boletus edulis*) mushroom by size exclusion liquid chromatography with sequential on-line UV-ICP-MS detection. *J Agric Food Chem.* 52:1315-1322.

Ysart G, Miller P, and Crews H. 1999. Dietary exposure estimates of 30 elements from the UK Total Diet Study. *Food Addit Contam.* 16:391-403.

### **Timetable**

19. Date when data could be submitted to JECFA

At next call for data for veterinary drugs. Study reports available, monographs would need to be prepared by Sponsor.

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

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