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
   $4\text{Bi(NO}_3\text{)}(\text{OH})_2\cdot\text{BiO(OH)}$ (European Pharmacopoeia - Ph. Eur.) OR $\text{Bi}_5\text{O(OH)}_9(\text{NO}_3\text{)}_4$

6. CHEMICAL STRUCTURE
   BSN has a 3 dimensional structure that consist of two basic units.
   Unit A is $\text{BiO(OH)}$

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

   \[
   \begin{array}{c}
   \text{B} \\
   | \\
   \text{B} - \text{A} - \text{B} \\
   | \\
   \text{B}
   \end{array}
   \]

   $4\text{Bi(NO}_3\text{)}(\text{OH})_2\cdot\text{BiO(OH)}$ (European Pharmacopoeia - Ph. Eur.) OR $\text{Bi}_5\text{O(OH)}_9(\text{NO}_3\text{)}_4$

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

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

* Table 5 of MRL Standard 2012


*** 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)


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.


**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.