

**Finding of No Significant Impact (FONSI)**  
for  
**Safe-Guard® AquaSol**  
**(fenbendazole oral suspension)**  
in  
**laying hens and replacement chickens**  
**intended to become laying hens**  
for  
**the treatment and control of adult**  
***Ascaridia galli* and *Heterakis gallinarum***

**Intervet Inc.**  
**Madison, NJ**

The Center for Veterinary Medicine (CVM) has considered the potential environmental impact of this action and has concluded that this action will not have a significant impact on the quality of the human environment and, therefore, an environmental impact statement will not be prepared.

Intervet Inc., d/b/a Merck Animal Health, is requesting the approval of a new animal drug application (NADA) for the use of Safe-Guard® AquaSol (fenbendazole oral suspension) for the treatment and control of adult *Ascaridia galli* and *Heterakis gallinarum* in laying hens and replacement chickens intended to become laying hens. Safe-Guard® AquaSol will be administered in drinking water at a dose of 1.0 mg/kg body weight (bw) for five consecutive days for a total dose of 5.0 mg/kg bw. Safe-Guard® AquaSol will be dispensed over the counter.

In support of the application, Intervet Inc. has provided an environmental assessment (EA) dated January 27, 2015. A copy of the EA is attached. The EA assesses the fate and effects of fenbendazole (FBZ) and its primary and secondary metabolites, oxfendazole (OXF) and fenbendazole sulfone (FBZ-SO<sub>2</sub>). The EA includes an exposure assessment from which predicted environmental concentrations (PECs) were calculated, an effects assessment from which the predicted no effects concentrations (PNECs) were derived, and a risk characterization that utilizes a risk quotient (RQ) method using the PEC/PNEC ratio.

The indication in the EA states that the product is "for the removal of the nematode parasites *Ascaridia galli* and *Heterakis gallinarum* in chicken." This indication differs from the indications being approved because the indication was changed after the EA was prepared. However, this will not change the results and conclusion of the EA because the analysis in the EA conservatively assumed that all classes of chickens on a farm will be treated, including laying hens. Therefore, the EA adequately evaluated the proposed indication for the supplemental approval of Safe-Guard® AquaSol in laying hens and replacement chickens intended to become laying hens.

## Risk Assessment Approach

The environmental fate of the three main compounds of concern (FBZ, OXF, and FBZ-SO<sub>2</sub>) is addressed in the EA and an initial PEC in soil (PEC<sub>soil</sub>) was calculated for each compound. Although traditionally accepted methods were used to calculate the PEC<sub>soil</sub> and PEC in water (PEC<sub>water</sub>) for FBZ, a more complex approach was used for OXF and FBZ-SO<sub>2</sub>. Experimental fate data suggest that, unlike FBZ, OXF and FBZ-SO<sub>2</sub> have the potential to persist and accumulate in the environment. Therefore, plateau PEC<sub>soil</sub> values were calculated for OXF and FBZ-SO<sub>2</sub> to account for the possibility of accumulation in the environment following several successive years of application of manure containing these compounds to agricultural fields. While effects data were generated for FBZ and OXF, they were not generated for FBZ-SO<sub>2</sub> because FBZ-SO<sub>2</sub> is a metabolite of OXF, i.e., a secondary metabolite of FBZ. Therefore, because there were no effects data with which to calculate PNECs and RQs for FBZ-SO<sub>2</sub>, a total residue approach was used for OXF and FBZ-SO<sub>2</sub> whereby individual plateau PEC<sub>soil</sub> values for OXF and FBZ-SO<sub>2</sub> were added together (OXF/FBZ-SO<sub>2</sub>) as a combined plateau PEC<sub>soil</sub> and it was assumed that FBZ-SO<sub>2</sub> is as toxic as OXF. This combined plateau value was then used to calculate the PEC<sub>water</sub> for OXF/FBZ-SO<sub>2</sub> and to calculate RQs. In the risk characterization section of the EA, separate RQs were calculated for FBZ and OXF/FBZ-SO<sub>2</sub>. To account for the presence of all three compounds in the soil simultaneously, the two RQs were ultimately added together for a total combined RQ value for each tested organism. We based our regulatory decision on these combined RQ values. Subsequent to preparation of the EA, an updated literature search was also conducted on May 15, 2017, and October 27, 2017. Based on results of the literature search, no information was identified that would change the current risk characterization and conclusions.

## Exposure Assessment

The exposure assessment in the EA contains the physical-chemical properties of FBZ, OXF, and FBZ-SO<sub>2</sub>, as well as soil adsorption/desorption and soil biodegradation data. The fate data suggested that FBZ is slightly to hardly mobile<sup>1</sup> while OXF and FBZ-SO<sub>2</sub> are considered to be moderately to slightly mobile. Additionally, the dissipation half-life (DT<sub>50</sub>) for FBZ ranges from 7.6 to 11.4 days while the DT<sub>50</sub> for OXF ranges from 123.1 to 319.4 days (three soil types: clay loam, loamy sand, and sandy loam tested). The DT<sub>50</sub> for FBZ-SO<sub>2</sub> was estimated to be 186.5 and 221.3 days based on the United States Environmental Protection Agency's EPI Suite program KOCWIN (v2.00).

No metabolism data were used in the EA to support the breakdown of FBZ in chickens prior to excretion. It was conservatively assumed that the 100% of the administered dose was excreted as FBZ and that, once in the soil, FBZ degrades to OXF which will then further degrade to FBZ-SO<sub>2</sub>. In addition, it was assumed that the maximum fraction of OXF and FBZ-SO<sub>2</sub> in the soil was the same, 64.2% of the original FBZ dose. Based on the expected use of Safe-Guard<sup>®</sup> AquaSol, the initial PEC<sub>soil</sub> and PEC<sub>water</sub> for FBZ were estimated to be 12.55 µg/kg and 0.14 µg/L, respectively. The initial PEC<sub>soil</sub> for OXF and FBZ-SO<sub>2</sub> were 26.74 and 12.88 µg/kg, respectively. These initial PEC<sub>soil</sub> values for OXF and FBZ-SO<sub>2</sub> were then refined to account for accumulation in the soil over time and added together for a single plateau PEC<sub>soil</sub>. The combined plateau PEC<sub>soil</sub> and PEC<sub>water</sub> for OXF/FBZ-SO<sub>2</sub> were estimated to be 39.62 µg/kg and 0.44 µg/L, respectively. No refinements were used to reduce the

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<sup>1</sup> Mobility classification is based on the Food and Agriculture Organization (FAO) Mobility Classification in the EPA's Guidance for Reporting on the Environmental Fate and Transport of the Stressors of Concern in Problem Formulations (December 2009). <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-reporting-environmental-fate-and-transport>, accessed December 13, 2016.

PEC<sub>soil</sub> for FBZ or OXF/FBZ-SO<sub>2</sub> to account for metabolism in the animal, or degradation in the soil, water, or manure. However, the PEC<sub>water</sub> was refined to account for adsorption to sediment. Thus, the refined PEC<sub>water</sub> for FBZ and OXF/FBZ-SO<sub>2</sub> were estimated to be 0.014 µg/L and 0.34 µg/L, respectively.

### Effects Assessment

In the effects assessment, Tier A (acute) PNEC values were derived for FBZ and OXF based on the effects in terrestrial (soil microorganisms, plants, and earthworms) and aquatic organisms (algae, *Daphnia magna*, and fish). PNEC values were derived using an effects endpoint divided by an assessment factor (AF), as recommended in CVM Guidance for Industry 166. However, the Tier A PNEC value for fish was calculated using the results from a prolonged fish toxicity test (i.e., 21-day median lethal concentration [LC<sub>50</sub>] and an AF of 100) instead of the traditionally accepted endpoint for fish, a 96-h LC<sub>50</sub>, and an AF of 1,000. This approach was used because the results of the prolonged toxicity test with FBZ suggested that it could take up to seven days for FBZ to come to equilibrium in the fish, resulting in a delay in toxic effects, due to its low water solubility (i.e., ~80 µg/L). A traditional 96-h acute study would not capture this observed latent toxicity and would potentially underestimate the true effects concentration. A prolonged latent toxicity test was not conducted for OXF because it does not have a low water solubility like FBZ and a 96-h LC<sub>50</sub> test was considered adequate to address the acute effects in fish. Tier B (chronic) PNEC values for *D. magna* were derived for FBZ and OXF by dividing the no observed effects concentration (NOEC) by AFs of 10 and 20, respectively. A more conservative approach was used for deriving the PNEC for *D. magna* exposed to OXF because, during the study, *D. magna* were fed three-times the amount recommended in the Organization for Economic Co-operation and Development Guideline 211 for this test. This deviation may have increased the observed NOEC for reproduction; therefore, an AF of 20 was used instead of the standard AF of 10 to account for this uncertainty.

### Risk Characterization

As described above, separate RQs were calculated for FBZ and OXF/FBZ-SO<sub>2</sub>. The RQs were added together to generate a combined RQ value for each organism and account for the presence of all three compounds in the soil simultaneously. This is a highly conservative approach because it assumes that the mode of action of all three compounds is the same. Tier A combined RQs were less than one for terrestrial organisms (i.e., RQs for plants and earthworms were 0.23 and 0.04, respectively); therefore, Tier B studies were not needed for terrestrial organisms. Tier A combined RQs for aquatic organisms calculated with the refined PEC<sub>water</sub>, were less than one for algae (0.009) and fish (0.29) but greater than one for *D. magna* (7.32). Consequently, Tier B studies were conducted on *D. magna* using chronic exposures of FBZ and OXF. Based on the results of the refined PEC<sub>water</sub> and Tier B effects study, the combined RQ for *D. magna* was 0.42. The effects on sediment-dwelling invertebrates was considered and the RQ for these invertebrates was also 0.42. Therefore, RQs for all organisms were less than one, indicating that FBZ will not present a significant risk to the environment. Additionally, considering the high degree of conservatism throughout the EA, it is likely that the environmental concentrations of FBZ and its metabolites are lower than has been predicted in this EA.

## Cumulative Assessment

In terms of cumulative impacts, we considered several possible scenarios that could occur: (1) use of FBZ for multiple indications in the same animals on the same farm, (2) use of FBZ in different species on the same farm, and (3) use of FBZ in the same or different species on different farms in the same watershed.

To evaluate these scenarios, CVM considered the potential for the environmental introduction of FBZ from multiple approved animal drug products containing FBZ (i.e., Safe-Guard® Type A Medicated Article, Safe-Guard® Suspension 10%, Panacur® Suspension 10%, Safe-Guard® 10% Paste, Panacur® 10% Paste, and Safe-Guard® Enproal medicated feed block). For comparison purposes, maximum PEC<sub>soil</sub> values from use of FBZ in beef cattle, dairy cattle, turkeys, and swine were calculated by CVM to be 25.3, 26.1, 31.0 and 45.6 µg/kg soil, respectively, based on the methods used in the current EA for use of Safe-Guard® AquaSol in chickens. Based on this analysis, Safe-Guard® Type A Medicated Article for swine would result in the highest PEC<sub>soil</sub> (45.6 µg/kg) and highest refined PEC<sub>water</sub> (0.05 µg/L) compared to all other FBZ products, including Safe-Guard® AquaSol for chickens (PEC<sub>soil</sub> = 12.55 µg/kg). Using the refined PEC<sub>water</sub> value and the effects data for *D. magna*, the RQ for Safe-Guard® Type A Medicated Article would be higher than the RQ for Safe-Guard® AquaSol (i.e., the RQ would be 1.5 versus 0.42). However, like the RQ value for Safe-Guard® AquaSol, we think that this value is an overestimation due to the conservative assumptions used to calculate the PEC values. The RQ value would likely be lower when metabolism in the target animal, adsorption in the soil, and degradation in the soil, water, and manure environments are considered.

For the first scenario, we considered the potential use of FBZ for multiple indications in the same animals on the same farm. This scenario is not expected to occur for chickens because Safe-Guard® AquaSol is the first approved FBZ product for use in chickens.

For the second and third scenarios, we considered the use of multiple FBZ drug products in different species on the same farm and on different farms in the same watershed. Based on our analysis, the use of Safe-Guard® Type A Medicated Article in swine will result in the highest PEC<sub>soil</sub> and PEC<sub>water</sub>; therefore, the use of this product alone represents the highest risk for environmental impacts. This is true for both a farm scale and a watershed scale type of analysis. For example, if all the swine on a farm or in a watershed were administered Safe-Guard® Type A Medicated Article, it would result in the highest surface water concentrations and pose the greatest risk to *D. magna*. However, if there were animal species, other than swine, that were administered FBZ on the same farm or on different farms in the same watershed, then the concentrations of FBZ entering surface waters would be lower, thereby reducing this risk. The risk would be lower because the FBZ products administered to the different species would result in lower PEC<sub>soil</sub> and PEC<sub>water</sub> values than that of Safe-Guard® Type A Medicated Article for swine. As a result, the RQ of 1.5 for *D. magna* for Safe-Guard® Type A Medicated Article will be the highest RQ for any type of FBZ exposure, cumulative or otherwise, at either the farm or watershed scale. Based on the conservative assumptions used in calculating the PEC and RQ values, it is concluded that runoff from any combination of approved uses of FBZ will not pose a substantial risk to non-target organisms at a farm scale or within a watershed.

## Regulatory Conclusion

Based on the information and analysis described in the EA and FONSI, including risk quotients for sensitive terrestrial and aquatic species, and also the updated literature

search, CVM has determined that no significant impacts on the human environment are expected from the proposed use of Safe-Guard® AquaSol (fenbendazole oral suspension) for the treatment and control of adult *Ascaridia galli* and *Heterakis gallinarum* in laying hens and replacement chickens intended to become laying hens.

*{ see appended electronic signature page }*

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## Electronic Signature Addendum for Submission ID

Signing Authority (Role)	Letter Date
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