Finding of No Significant Impact (FONSI)
for

SAFE-GUARD AQUASOL
(fenbendazole oral suspension)
in
Chickens

Intervet Inc.
d/b/a Merck Animal Health
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. is requesting the approval of a new animal drug application (NADA) for the use of SAFE-GUARD AQUASOL (fenbendazole oral suspension)[1] for the treatment and control of adult *Ascaridia galli* in broiler chickens and replacement chickens intended to become breeding chickens and for the treatment and control of adult *Ascaridia galli* and *Heterakis gallinarum* in breeding chickens. 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. We have reviewed the EA and find that it supports a FONSI.

The EA assesses the fate and effects of fenbendazole (FBZ) and its principle primary and secondary metabolites, oxfendazole (OXF) and fenbendazole sulfone (FBZ-SO_2), respectively. 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 CVM finalized these indications after the EA was prepared. Additionally, the current proposed indications for SAFE-GUARD AQUASOL do not include use in laying hens or replacement chickens intended to become laying hens even though the evaluation in the EA considers use of FBZ in all classes of chickens, including laying hens. The analysis in the EA conservatively assumed that all chickens on a farm will be treated regardless of the class of chicken. The EA is also conservative in that laying hens represent the class of chickens producing the highest exposure concentrations, and thus the highest potential risk. Therefore, the EA is considered to have adequately evaluated all proposed indications for the original approval of SAFE-GUARD AQUASOL in chickens.

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[1] The established name for the drug in the EA (20% fenbendazole suspension) differs from that on the product label and FONSI (fenbendazole oral suspension) because it was changed to comply with the United States Pharmacopeia (USP) nomenclature policy after the EA was prepared.

Risk Assessment Approach

The environmental fate of the three main compounds of concern (FBZ, OXF, and FBZ-SO_2) is addressed in the EA and an initial PEC in soil (PEC_{soil}) was calculated for each compound. Although traditionally accepted methods were used to calculate the PEC_{soil} and PEC in water (PEC_{water}) for FBZ, a more complex approach was used for OXF and FBZ-SO_2. Experimental fate data suggest that, unlike FBZ, OXF and FBZ-SO_2 have the potential to persist and accumulate in the environment. Therefore, plateau PEC_{soil} values were calculated for OXF and FBZ-SO_2 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_2 because FBZ-SO_2 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_2, a total residue approach was used for OXF and FBZ-SO_2 whereby individual plateau PEC_{soil} values for OXF and FBZ-SO_2 were added together (OXF/FBZ-SO_2) as a combined plateau PEC_{soil} and it was assumed that FBZ-SO_2 is as toxic as OXF. This combined plateau value was then used to calculate the PEC_{water} for OXF/FBZ-SO_2 and to calculate RQs. In the risk characterization section of the EA, separate RQs were calculated for FBZ and OXF/FBZ-SO_2. 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.

Exposure Assessment

The exposure assessment in the EA contains the physical-chemical properties of FBZ, OXF, and FBZ-SO_2, as well as soil adsorption/desorption and soil biodegradation data. The fate data suggested that FBZ is slightly to hardly mobile[2] while OXF and FBZ-SO_2 are considered to be moderately to slightly mobile. Additionally, the dissipation half-life (DT_{50}) for FBZ ranges from 7.6 to 11.4 days (three soil types) while the DT_{50} for OXF ranges from 123.1 to 319.4 days (three soil types) and the DT_{50} for FBZ-SO_2 was estimated to be 186.5 and 221.3 days (two soil types).

No metabolism data was 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_2. In addition, it was assumed that the maximum fraction of OXF and FBZ-SO_2 in the soil were the same, 64.2% of the original FBZ dose. Based on the expected use of SAFE-GUARD AQUASOL, the initial PEC_{soil} and PEC_{water} for FBZ were estimated to be 12.55 µg/kg and 0.14 µg/L, respectively. The initial PEC_{soil} for OXF and FBZ-SO_2 were 26.74 and 12.88 µg/kg, respectively. These PEC_{soil} values for OXF and FBZ-SO_2 were then refined to account for accumulation in the soil over time and added together for a single plateau PEC_{soil}. The combined plateau PEC_{soil} and PEC_{water} for OXF/FBZ-SO_2 were estimated to be 39.62 µg/kg and 0.44 µg/L, respectively. No refinements were used to reduce the PEC_{soil} for FBZ or OXF/FBZ-SO_2 to account for metabolism in the animal, or degradation in the soil, water, or manure. However, the PEC_{water} was refined to account for strong adsorption to sediment. Thus, the refined PEC_{water} for FBZ and OXF/FBZ-SO_2 were estimated to be 0.014 µg/L and 0.34 µg/L, respectively.

[2] 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).
http://www.epa.gov/pesticides/science/efed/policy_guidance/team_authors/endangered_species_reregistration_workgroup/esa_reporting_fate.htm

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 (GFI) 166. However, the Tier A PNEC value for fish was calculated using the results of a prolonged fish toxicity test (i.e., 21-day median lethal concentration [LC_{50}] and an AF of 100) instead of the traditionally accepted endpoint for fish, a 96-h LC_{50}, 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_{50} 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 (OECD) 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_2. The RQs were ultimately 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. No refinements were used to reduce the PEC_{soil}, but adsorption data were used to reduce the PEC_{water}. 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_{water}, 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 exposing *D. magna* to chronic exposures of FBZ and OXF. Based on the results of the refined PEC_{water} 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 conservativism 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_{soil} 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_{soil} (45.6 µg/kg) and highest refined PEC_{water} (0.05 µg/L) compared to all other FBZ products, including SAFE-GUARD AQUASOL for chickens (PEC_{soil} = 12.55 µg/kg). Using the refined PEC_{water} 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_{soil} and PEC_{water}; 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 animals on a farm or in a watershed were swine 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_{soil} and PEC_{water} 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, CVM has determined that no significant impacts on the human environment are expected from the proposed use of SAFE-GUARD AQUASOL (fenbendazole oral suspension) in chicken for the proposed indications.

{see appended electronic signature page}

Steven D. Vaughn, DVM
Director, Office of New Animal Drug Evaluation, HFV- 100
Center for Veterinary Medicine
U.S. Food and Drug Administration

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Signing Authority (Role)	Letter Date
Steven Vaughn (Office Director)	4/22/2015

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