Finding of No Significant Impact (FONSI)

In support of the supplemental approval of a new animal drug application (NADA)
for
increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNVOEX® Choice (trenbolone acetate and estradiol benzoate) is the first implant and a SYNOVEX® Choice, SYNOVEX® Plus, or SYNOVEX® ONE Feedlot implant is administered 60 to 120 days later,
and for
increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX® Choice is the first implant and a SYNOVEX® Plus implant is administered 60 to 120 days later

Zoetis Inc
Kalamazoo, MI

The Center for Veterinary Medicine (CVM) has thoroughly evaluated the potential environmental impact of this action (the supplemental approval of SYNOVEX® Choice, SYNOVEX® Plus, and SYNOVEX® ONE Feedlot in reimplant programs) 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.

Zoetis Inc (Zoetis) is requesting the supplemental approval of a new animal drug application (NADA) for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX® Choice (trenbolone acetate and estradiol benzoate) is the first implant and a SYNOVEX® Choice, SYNOVEX® Plus, or SYNOVEX® ONE Feedlot implant is administered 60 to 120 days later, and for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX® Choice is the first implant and a SYNOVEX® Plus implant is administered 60 to 120 days later. SYNOVEX® Choice, SYNOVEX® Plus, and SYNOVEX® ONE Feedlot are administered by subcutaneous implantation in the middle-third of the ear. SYNOVEX® Choice contains a total of 100 mg trenbolone acetate and 14 mg estradiol benzoate in four uncoated pellets; SYNOVEX® Plus contains 200 mg trenbolone acetate and 28 mg estradiol benzoate in eight uncoated pellets; and SYNOVEX® ONE Feedlot contains 200 mg trenbolone acetate and 28 mg estradiol benzoate in eight extended-release (coated) pellets. These products are dispensed over the counter.

In support of the application, Zoetis has provided an Environmental Assessment (EA) dated April 21, 2022 (hereafter, referred to as the 2022 EA). A copy of the 2022 EA is attached. Prior to the submission of the 2022 EA, CVM provided guidance to and assisted Zoetis by outlining the types of environmental information required for inclusion in the 2022 EA. CVM independently evaluated the 2022 EA to ensure the scope and content were adequate and to ensure that the information presented in the EA was accurate. CVM determined that the 2022 EA provides sufficient evidence to support a FONSI.

The 2022 EA evaluates the risk for significant environmental impacts to occur due to exposure of freshwater fish to the six major metabolites of trenbolone acetate and estradiol benzoate (i.e., 17α-trenbolone, 17β-trenbolone, trendione, and 17α-estradiol, 17β-estradiol, estrone, respectively). The 2022 EA contains an exposure assessment, effects assessment, and risk characterization. The 2022 EA follows a similar risk assessment approach, and uses many of the same assumptions, as that described in the EA prepared for the original NADA of SYNOVEX® ONE Feedlot and Grass, dated May 29, 2014 (hereafter, referred to as the 2014 EA).[1] A summary of the 2014 EA is provided in Section 3, "*Risk Assessment Approach*," of the 2022 EA. The 2022 EA also includes new environmental fate modeling and additional information obtained since the 2014 EA. A summary of the 2022 EA, including the new environmental fate modeling and additional information, is provided below.

In the exposure assessment, four exposure routes were evaluated: (1) runoff from feedlot surfaces, (2) runoff from manure amended to croplands, (3) runoff from cropland irrigated with liquid manure, and (4) runoff excreted onto pastureland. Due to the complexity in conducting environmental fate modeling of the six major metabolites of trenbolone acetate and estradiol benzoate, a surrogate compound approach was used. This approach conservatively defined a single surrogate trenbolone compound and a single surrogate estradiol compound using the physical-chemical and environmental fate properties of the six major metabolites.

Two different environmental fate models, a modified version of the European version of the Pesticide Root Zone Model (winPRZM) and the Variable Volume Water Model (VVWM), were used to estimate the predicted environmental concentration (PEC) values of the surrogate trenbolone compound and surrogate estradiol compound in water from runoff and erosion of liquid and solid manure applied to cropland, and to simulate their fate on a feedlot. These environmental fate models are validated models currently used by two regulatory authorities [i.e., winPRZM is a validated model used by the European Medicines Agency and VVWM is a validated model used by the United States (US) Environmental Protection Agency] to evaluate the risk of chemical residues in the environment. The modifications made to winPRZM were intended to improve the realism of the model, as compared to the 2014 EA, by incorporating typical feedlot practices that could alter the distribution of the surrogate trenbolone compound and surrogate estradiol compound. These modifications include the simulation of manure buildup on and regular manure scraping of the feedlot.

The environmental fate of the surrogate trenbolone compound and surrogate estradiol compound were evaluated in the 2022 EA for a worst-case scenario, the Lyon/Sioux watershed in IA. In the 2014 EA, the potential impacts of SYNOVEX® ONE were evaluated in five regions of the US with the highest number and density of beef cattle, including 1) Lyon and Sioux Counties, IA; 2) Castro County, TX 3) Mercer County, OH; 4) Huron County, MI, and 5) Lancaster County, PA. The 2014 EA found that the Lyon/Sioux watershed in IA consistently resulted in the highest PEC values, and thus, was considered the worst-case scenario. Based on updated information included in Appendix 3.3 of the 2022 EA, the Lyon/Sioux watershed in IA remains the worst-case scenario, and was therefore used as a single nationwide representative worst-case watershed. In addition, the maximum fraction of animal feeding operations (AFO) with direct discharge to surface waters was assumed to be 25% of the AFOs in a watershed. As noted in the 2022 EA, it is likely that this value overestimates the percentage of AFOs with direct discharge to surface waters because new

[1] The EA prepared for the original NADA of SYNOVEX® ONE Feedlot and Grass is titled, "Environmental Assessment for SYNOVEX® ONE (Estradiol Benzoate and Trenbolone Acetate Extended Release Implant) Feedlot and Grass for Beef Steers and Heifers." The SYNOVEX® ONE EA and FONSI can be accessed at FDA's Animal Drugs at FDA website: https://animaldrugsatfda.fda.gov/adafda/views/#/environmentalAssessments

regulatory requirements and best management practices (BMP) have been implemented since the data used to estimate this value was collected (e.g., 1997). In addition, since 1997, the number of AFOs has decreased by 74%, thereby reducing the number of AFOs that have the potential to discharge.

Based on the assumptions identified above, hundreds of PEC values were estimated for several SYNOVEX® reimplant scenarios (see Appendix 7, Tables 32 and 33), over a 30-year simulation using the Lyon/Sioux watershed in IA. To determine whether the PEC values would result in significant environmental impacts, an effects assessment and risk characterization were conducted.

In the effects assessment, predicted no effects concentration (PNEC) values for freshwater fish were calculated for the most potent metabolites (i.e., 17α-trenbolone, 17β-trenbolone, 17α-estradiol, and 17β-estradiol). Steroid hormones, such as trenbolone and estradiol, are known endocrine disrupting compounds that can affect sexual differentiation and reproduction of fish and amphibians at low concentrations. In the 2014 EA, reproductive endpoints (fecundity, fertilization, and sex ratio) in fish were found to be the most sensitive endpoints (i.e., lowest effects values); thus, data from fish reproduction studies were used to estimate the PNEC values. The PNEC values were derived using the most conservative no observed effects concentrations (NOEC) or effects concentrations that resulted in a 10% decrease in reproduction (EC_{10}) for the most sensitive fish reproduction endpoints estimated from chronic toxicity studies (≥21 days). The effects concentrations (NOEC or EC_{10}) were divided by an assessment factor (AF), as recommended in CVM Guidance for Industry #166,[2] to calculate the PNEC. The AF is intended to cover the need to extrapolate from laboratory study results to the field, and uncertainties such as intra- and inter-laboratory differences and species variation. Therefore, although the PNEC values utilized in the 2022 EA were derived from effects data reported for fish (the most sensitive aquatic organism evaluated in the 2022 EA), they should also be protective of all aquatic organisms, including threatened and endangered species and their critical habitat. The PNEC values were reported as 3.2, 25, and 1.4 ng/L for 17α-trenbolone, 17α-estradiol, and 17β-estradiol, respectively. A range of PNEC values between 0.25 and 0.5 ng/L was derived for 17β-trenbolone. A detailed explanation for the derivation of these values is provided in the 2014 EA. New literature searches conducted by Zoetis and CVM did not identify any new effects data that was more sensitive than that used to derive the PNEC values in the 2014 EA. Therefore, the same PNEC values were used in the 2022 EA.

The 2022 EA evaluated the potential for significant environmental impacts using the risk quotient (RQ) method. An RQ value is calculated by dividing the PEC value by the PNEC value. A threshold value ≥1.0 indicates the potential for environmental impacts. For the surrogate estradiol compound, the toxicity was conservatively assumed to be equal to 17β-estradiol, the most potent metabolite [i.e., the PEC value for the surrogate estradiol compound was compared to the PNEC of 17β-estradiol (1.4 ng/L)]. For the surrogate trenbolone compound, a different approach was used, in which, the PEC value was proportioned based on the relative distribution of 17α-trenbolone and 17β-trenbolone expected to enter the environment from the urine and feces of cattle administered a SYNOVEX® implant. In order to determine the relative distribution of 17α-trenbolone and 17β-trenbolone, Zoetis conducted a cattle excretion study using radiolabeled trenbolone acetate (^{14}C-trenbolone acetate), and conducted several androgen receptor transactivation assays (ARTA) (see Section 10 and Appendix 4 of the 2022 EA). The results of the Zoetis-

[2] CVM Guidance for Industry #166. 2006. Environmental Impact Assessments (EIAs) for Veterinary Medicinal Products (VMPs) – Phase II. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-166-vich-gl38-environmental-impact-assessments-eias-veterinary-medicinal-products-vmps-phase

owned studies were compared to those described in the published literature. Based on the weight of evidence, these studies supported that 95% of the surrogate trenbolone compound should be attributed to 17α-trenbolone, while 5% should be attributed to 17β-trenbolone. Therefore, 95% of the PEC value for the surrogate trenbolone compound was attributed to 17α-trenbolone, and the remaining 5% to 17β-trenbolone. The corresponding PEC values were then divided by the PNEC to determine the RQ values for the surrogate trenbolone compound.

In total, hundreds of RQ values were estimated for the surrogate estradiol compound and surrogate trenbolone compound. A complete list of the RQ values for the surrogate estradiol compound is provided in Table 16 (page 42), and for the surrogate trenbolone compound in Table 17 (page 44) of the 2022 EA. In all reimplant programs, the RQ values estimated for the surrogate estradiol compound were <1.0. The overall maximum RQ value for the surrogate estradiol compound was 0.11 and corresponded to the reimplant program wherein cattle are implanted initially with SYNOVEX® Plus followed by reimplantation with SYNOVEX® Plus 60 and 120 days later during a 201-day grow-out period on a feedlot.

All RQ values estimated for the surrogate trenbolone compound were <1.0, with the exception of two reimplant programs. The first was for a program in which an initial implantation of SYNOVEX® Plus is followed by a reimplantation using SYNOVEX® Plus 60 days later during a 117 day grow-out period. This program resulted in an RQ value equal to 1.0 for one day over the entire 30-year simulation. The second reimplant program to result in an RQ value >1.0 was a program in which cattle are initially implanted with SYNOVEX® Plus, followed by two reimplantations with SYNOVEX® Plus 60 and 120 days later during a 177-day grow-out period on a feedlot. This program resulted in one 8-day period, over the entire 30-year simulation, where RQ values were >1.0. The average and maximum RQ values over the 8-day period were 1.05 and 1.11, respectively.

In addition, the 2022 EA also includes a cumulative exposure analysis that evaluates the potential for significant environmental impacts from the introduction of steroid hormones in the environment from multiple sources, including both natural and anthropogenic sources (e.g., excretion by humans, livestock) (see Section 14 of the 2022 EA). This evaluation relies on the cumulative exposure assessment described in the 2014 EA, in which, the maximum PEC values associated with the use of SYNOVEX® ONE Feedlot and Grass were compared to the overall load of steroid hormones estimated to be present in the environment as a result of both natural and anthropogenic sources. Based on a similar comparison to the PEC values estimated from the use of SYNOVEX® implants in reimplant programs, the overall load of steroid hormones entering the environment from this use are expected to be 1% (or less) than that from natural and anthropogenic sources collectively.

All of the RQ values reported in the 2022 EA are expected to be an overestimation of the potential environmental risk from the proposed use because they were estimated based on several conservative assumptions. For example:

- It was assumed that 25% of AFOs are directly discharging to surface waters, which is likely an overestimate because it is based on data collected 25 years ago and it is expected that most AFOs are now in compliance with the Clean Water Act;

- The assumption that 5% of the surrogate trenbolone compound is attributed to 17β-trenbolone is likely an overestimate because, as demonstrated by ARTA analyses conducted by Zoetis, all trenbolone acetate metabolites collectively present in urine and feces of cattle administered SYNOVEX® implants are less potent, and therefore, expected to be less toxic, than 17β-trenbolone as a single metabolite; and

- The PNEC values were derived by dividing conservative endpoints for the most sensitive species by an assessment factor (AF).

Several additional conservative assumptions were considered in the 2022 EA (see Section 15), which collectively contribute to an overestimation of the risk to the environment. Thus, it is expected that all RQ values for the surrogate trenbolone compound and estradiol compound are <1.0.

Based on CVM's evaluation and analysis of the information provided in the 2022 EA, CVM made the finding that the action to approve the supplemental NADA for use of SYNOVEX® Choice, SYNOVEX® Plus, and SYNOVEX® ONE Feedlot in reimplant programs would not individually or cumulatively have a significant effect on the quality of the human environment in the US. Based on that finding, CVM has decided not to prepare an environmental impact statement for this proposed action.

{see appended electronic signature page}

Matthew Lucia, DVM
Director
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
U.S. Food and Drug Administration

Electronic Signature
Addendum for Submission ID

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