DATE OUT: 12/08/2010

SUBJECT: **PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]**
DP BARCODE No.: D370437 **Symbol No.:** 86833-R
PRODUCT NAME: ZONASTAT-H
COMPANY: Humane Society of the United States
FOOD USE [ ] NON-FOOD USE [X] INTEGRATED FORMULATION [ ]
PCC: 176603 **DECISION No.** 420440 **ACTION CODE:** R110

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INTRODUCTION:

The registrant has submitted a registration application for the new restricted-use end-use product (EP) ZONASTAT-H. The EP is intended to be used as a contraceptive treatment to control wild horses and burros. The active ingredient (AI) is the porcine derived, glycoprotein ZP3. In support of the application, the applicant has submitted for review, product chemistry studies corresponding to guideline 830 series group A & group B (MRID No. 47859802). The registrant has also submitted a proposed CSF for basic formulation dated 09/16/2009 and the proposed product label. ARIA/RD has been asked to determine the acceptability of the product chemistry data submitted for the proposed end-use product and determine the acceptability of the proposed basic CSF.

SUMMARY OF FINDINGS

1. The proposed end-use produet is a restricted-use product that can only be administerd by certified applicators. The proposed product contains the glycoprotein ZP3 (unregistered source) as the AI with a label claim nominal concentration of 0.071% with a protein content no less than 100 µg AI/0.5 mL product. The toxicity review was conducted on and the proposed label claims that the end-use product is a two component

product of two vials, one containing the AI as listed on the CSF, the other containing an adjuvant emulsion.

2. The proposed CSF for basic formulation (dated 09-16-2009) is not filled out completely or correctly. The nominal concentration of the active ingredient as expressed on the CSF does not concur with the product label claim nominal concentration. The CSF only reports the AI component. Because the end-use product is a mixture of two components that must be used in conjunction, the CSF must contain the components of both vials to be mixed. The CSF is not in compliance with PR Notice 91-2. Only those inert ingredients present in the AI vial of the end-use product have been approved by the Agency for the proposed uses (IIAB, 10-06-09).

3. The certified limits proposed by the registrant for the active ingredient are not based on the standard certified limit table set forth in 40CFR§158.350(b)(2). The registrant has provided justifications (via e-mail with reviewer) for the proposed certified limits. The data and justifications submitted corresponding to guidelines 830.1750 (Certified Limits) satisfy the product chemistry data requirements of 40CFR§158.32 [MRID No. 47859802]. The CSF must be revised accordingly. The justifications provided by the registrant to the reviewer are detailed in the Confidential Appendix.

4. The data submitted corresponding to guidelines 830.1600 (description of material used to produce the product), 830.1650 (description of formulation process), 830.1670 (discussion on the formation of impurity) and 830.1750 (certified limits) satisfy the data requirements of 40CFR §158.325, §158.335, §158.340 and 158.350 respectively. The formulation / isolation of the AI (ZP3) is described in the Confidential Appendix.

5. The product chemistry data submitted corresponding to the guidelines 830 series group B (physical-chemical properties) satisfy the data requirements of 40CFR §158.310(e). A signed self-certification statement was provided for the physical-chemical properties. Although it says that the product is stable for up to 2 years, this data must be submitted to the Agency, or a new storage stability study and corrosion characteristics study must be completed and submitted to the Agency for review upon completion [MRID No. 47859802].

CONCLUSIONS:

ARIA has reviewed the product chemistry data submitted for the proposed end-use product and has concluded that:

1. The proposed CSF for basic formulation (dated 09-16-2009) is unacceptable. A revised CSF must be submitted to the Agency clearing up the discrepancies as listed in Finding 2 and the Confidential Appendix.

2. The data submitted corresponding to guidelines 830.1600 (description of materials used to produce the product), 830.1650 (description of formulation process), and

830.1670 (discussion on the formation of impurity), and 830.1750 (certified limits) are acceptable. The justifications provided for the proposed wider certified limits for a few of the inert ingredients are acceptable.

3. The data submitted corresponding to guidelines 830.1800 (enforcement analytical method) does not satisfy the guideline requirements for the traditional end-use product. However, based on the manufacturing procedure and formulation process, as well as the label (which will be revised to clearly indicate the batch number from which the sample vial was produced and clearly express a defined expiration date, for this product), the method submitted to determine the total protein concentration of the batch (from which the single use sample vial will be produced) is adequate for Agency purposes.

4. The product chemistry data submitted corresponding to reference guidelines 830 series group B (physical-chemical properties) are acceptable, with the exception of 830.6317 (storage stability) and 830.6320 (corrosion characteristics). One year study results for the guidelines 830.6317 (1 year storage stability) and 830.6320 (corrosion characteristics) must be submitted to the Agency for evaluation. As the end-use product has a two year expiration date listed on the label, the data for which this expiration date is based may be sufficient to satisfy guideline requirements.

Product Chemistry Data (Series 830 group A & group B)

Subgroup A	Data Required Fulfilled	MRID No.
830.1550. Chemical Identity (basic CSF)	U	CSF (dated 09/16/09)
830.1600. Beginning Materials	A	47859802
830.1650. Formulation Process	A	47859802 (and e-mail communication)
830.1670. Discussion of Impurities	A	47859802
830.1700. Preliminary Analysis	NA	47859802
830.1750. Certified Limits (basic CSF)	U	47859802 (and e-mail communication)
830.1800. Enforcement Analytical Method	A	e-mail communication with reviewer

Subgroup B	Data Required Fulfilled	Value or Qualitative Description	MRID No.
830.6302. Color	A	Clear	47859802
830.6303. Physical State	A	Aqueous solution or powder	47859802
830.6304. Odor	A	Odorless	47859802
830.6314. Oxidation/Reduction Action	A	Denatured by acid or base, no incompatibility	47859802
830.6315. Flammability	A	Nonflammable (protein)	47859802
830.6316. Explodability	A	Not explosive (protein)	47859802
830.6317. Storage stability	I	Frozen liquid or (or powder in desicant) is viable for 2 years.	47859802
830.6319. Miscibility	A	Complete in water.	47859802
830.6320. Corrosion Characteristics	I	No Corrosive activity.	47859802
830.6321. Dielectric Breakdown Voltage	NA		
830.7000. pH	A	7.0-704	47859802
830.7100. Viscosity	A	Aqueous form is the same as water.	47859802
830.7000. Relative Density	A	1.0 in water	478586-02
830.7520. Particle size, fibre length, & diameter distribution	NA		

Explanations: A = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

Confidential Appendix:

Composition:

1. The Toxicology review is based on the complete end-use product, the combination of two separate vials sold and mixed before use. The CSF must be revised to describe the end-use product as it will be administered. Therefore, the adjuvant (Modified Freund's Complete Adjuvant (mFCA) for primary injections and/or Freund's Incomplete Adjuvant (FIA) for booster injections) must be included on the CSF and the mass ratios of all components revised accordingly. The adjuvant and supplier of the adjuvant must be cleared by the IIAB for use in pesticide formulations.

2. The clarity of the CSF could be improved by stating the active ingredient in the following manner (Column 10) as a result, the corresponding boxes in columns 13 (a and b) and 14 (a and b) will require updating:

Porcine zona pellucid (PZP) containing:
Glycoprotein ZP3; no CAS Number or Name (71%)
Glycoproteins (ZP1, ZP2, ZP4); no CAS Numbers or Names (29%)

3. Box 17 should be revised to include the total weight as well as the total %.

Justifications for Certified Limits:

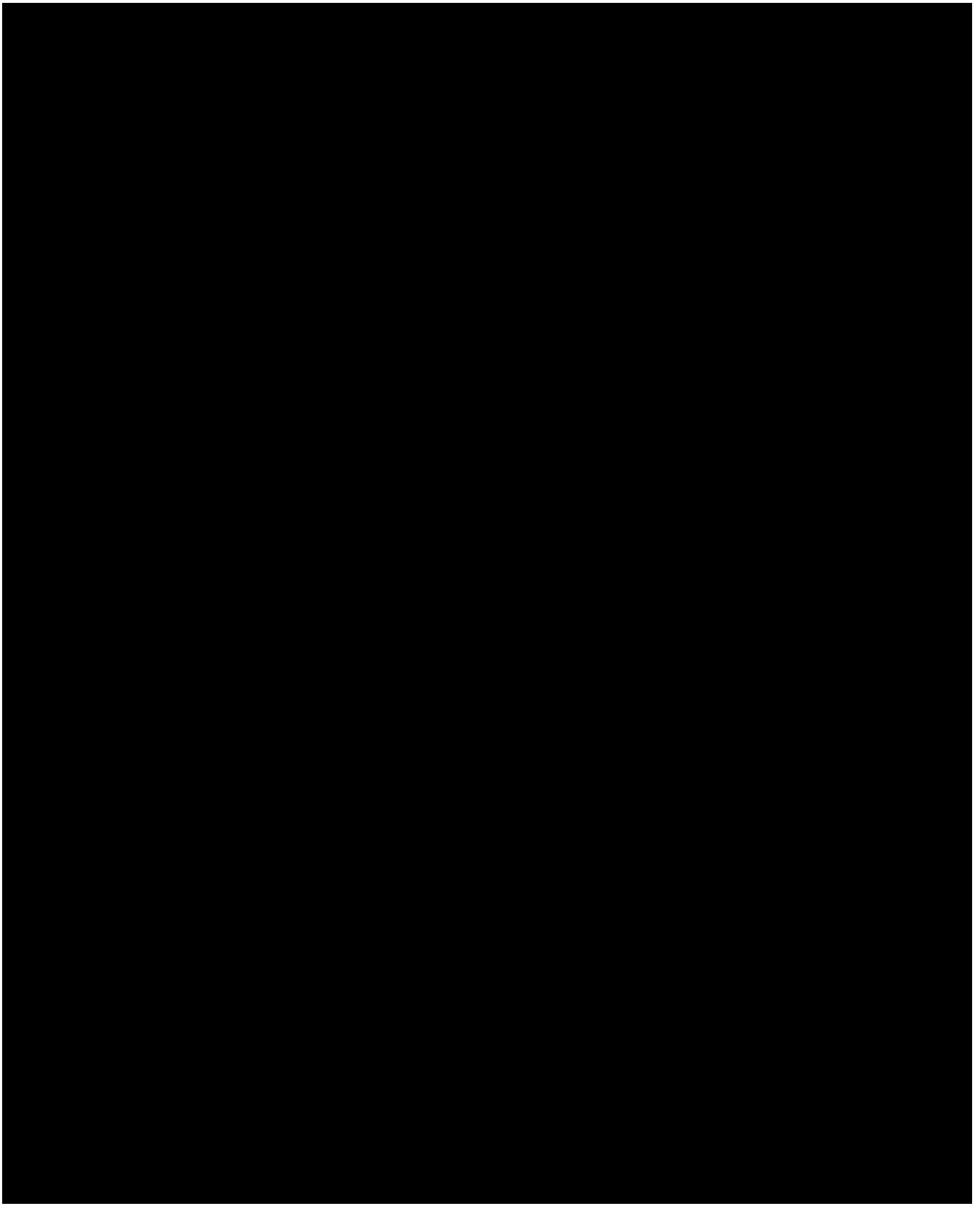
1. [redacted]

The CSF must be revised accordingly.

2. The lower certified limit of the carrier/solvent must be adjusted to be at least marginally lower than the nominal concentration.

Formulation and Production of the AI and single-dose vials:

Manufacturing process information may be entitled to confidential treatment



Manufacturing process information may be entitled to confidential treatment