ENVIRONMENTAL ASSESSMENT

1. Date: November 7, 1996
2. Name of applicant/petitioner: Ivy Laboratories, Inc.
3. Address: 8857 Bond
   Overland Park, KS 66214
4. Description of the proposed action:

Approval is requested for a supplemental New Animal Drug Application to NADA 110-315 which provides data to demonstrate the reproductive safety of IMPLUS-C brand of progesterone and estradiol benzoate implants when administered to heifers intended for reproductive use.

Should approval be granted, the statement on the IMPLUS-C label which reads: "Do not use in calves intended for reproduction, or in calves less than 45 days old" would be changed to read: "Do not use in bull calves intended for reproduction, or in calves less than 45 days old."

The net effect of this action would be to increase the use of IMPLUS-C in heifers intended for reproduction.

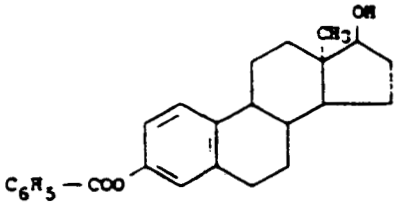
Since the active ingredients of IMPLUS-C are well-known naturally occurring sex steroids, this EA has been prepared pursuant to 21 CFR 25.31a(b)(5).

The product will be manufactured at the address listed in Item 3 above and will be distributed for use to calf producers throughout the U.S. The manufacturing facility is located in a light-industrial business park which is bounded by major highways to the east and west and retail shopping areas to the north and south. Calf producers are located in rural areas where animals are penned or pastured in typical feedlot or pasture environments.

5. Identification of chemical substances that are the subject of the proposed action:

Estradiol Benzoate:

Chemical Name: estra-1,3,5(10)-triene-3,17-diol (17β)-,3-benzoate
CAS Reg. No: [50-50-0]
Molecular Weight: 376.5
Molecular Formula: $C_{25}H_{28}O_3$
Structural Formula:

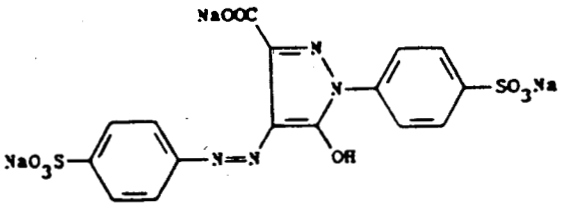


Physical Description: white or creamy white, odorless, crystalline powder

5. Identification of chemical substances that are the subject of the proposed action: (continued)

Progesterone:

Chemical Name: pregn-4-ene-3, 20-dione
CAS Reg. No: [57-83-0]
Molecular Weight: 312.51
Molecular Formula: $C_{21}H_{30}O_2$
Structural Formula:



Physical Description: White or creamy white, odorless, crystalline powder.

6. Introduction of substances into the environment:

This approval allows for the use of the active drug substances progesterone and estradiol benzoate in the production of the formulated product.

The particulate matter produced during manufacturing and packaging of this product is collected by a dust collection system. The system is not vented to the atmosphere and collected solids are placed in plastic bags and disposed of by established solid waste disposal methods. Any dust not collected by the dust collector is vacuumed, swept or mopped up daily. Liquids used in product processing are removed by oven drying and this effluent is vented to the atmosphere. Small quantities of solvents are used in cleaning production equipment. Water is used to mop production and packaging floors.

Plant personnel have been instructed in safe product handling practices and standard operating procedures and policies are in place to assure compliance. Workers are protected by rubber gloves, dust masks, head covers and uniforms, as is appropriate for the work activity.

The Federal, State and local emissions requirements are as follows:

Federal Regulations: The National Environmental Policy Act of 1969 (NEPA), PL 91-190, 83 Stat 853 (42 USC CFR 4332 as amended), 21 CFR Part 25, Environmental Impact Consideration; and CVM Environmental Assessment Technical Handbook;

6. Introduction of substances into the environment: (continued)

State of Kansas Regulations: "Solid Waste Management Act", Kansas Statutes, November 1995: Chapter 65, Article 34 (65-3401 to 65-3429); "Air Quality Control Act", Kansas Statutes, Chapter 65, Article 30 (65-3001 to 65-3027). Kansas State Department of Health and Environment, "Ambient Air Quality Standards and Air Pollution Control Regulations", Sections 28-19-7 to 28-19-753, as amended, January 25, 1995; "Water Quality Control Program", Sections 65-102a to 65-171u, as amended in 1995 Supplement

Local Regulations: The City of Overland Park, Kansas and Johnson County, Kansas defer to the state of Kansas Department of Health and Environment and its implementing regulations except in the case of Johnson County Unified Wastewater District which requires an Industrial Wastewater Discharge Limitation Permit. Ivy Laboratories, Inc. has been issued Permit No. 89TC110. The manufacturing facility is operated in compliance with the foregoing Federal, State and Local requirements.

Approval of the supplemental NADA allowing the use of IMPLUS-C in heifer calves intended for reproduction will have no material effect on the emissions from the production facility. We estimate that IMPLUS-C sales could increase by 10% as a result of this approval. Since the product is already being produced in the form of IMPLUS-S and IMPLUS-C brands of progesterone, estradiol benzoate implants with IMPLUS-C estimated to be no more than 10% of the IMPLUS-S production, the increase would result in IMPLUS-C production becoming 11% rather than 10% of total production.

7. Fate of emitted substances in the environment:

Use of IMPLUS-C in heifer calves intended for reproduction is not expected to alter significantly the concentration and distribution of the product, its metabolites, degradation products, or its constituent parts in the environment. The product will be administered in heifer calves in the same way as it is in other calves, as a subcutaneous ear implant. It is estimated that the increase in use of the product will be at most 10% of IMPLUS-C so this would be the expected increase in the other related factors.

8. Environmental effects of released substances:

Progesterone and estradiol and their metabolites are ubiquitous in the normal physiological environment of both human sexes as well as in the human food supply and their physiology, pharmacology and toxicology are well established. The sponsor is not aware of detrimental effects of the product to organisms in the environment such as fish, invertebrates, plants, fungi and bacteria. The use of this product will not increase the concentrations of the naturally occurring substances progesterone and estradiol in the environment.

9. Use of resources and energy:

Progesterone and estradiol benzoate are derived, by chemical transformation procedures, from plant sapogenins such as Hecogenin, from Agave-species; Diosgenin, from Dioscorea composita, D. terpinapensis; Stigmasterol, from soy or calabar beans; and many others. These plant sapogenins are in plentiful world supply.

The power (electrical energy) requirements for the manufacture of the finished dosage form of the product is not out of the ordinary requirement for pharmaceutical product production, and this energy supply is presently available in adequate amount.

There are no significant wastes generated from production, or use or disposal of the product and consequently no extraordinary use of energy is required.

10. Mitigation measures:

No adverse environmental impacts are anticipated as a result of the proposed action so no mitigation measures are needed.

11. Alternatives to the proposed action:

No potential adverse environmental impacts have been identified for the proposed action, thus no alternatives are needed.

12. List of preparer(s):

Gary D. Hindman, Ph.D.
Vice President & General Manager
Ivy Laboratories, Inc.
Ph.D. Analytical Chemistry
Eighteen years Veterinary
Pharmaceutical Industry
Consulted Charles Erikson of FDA's
Environmental Impact Staff

13. Certification:

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Date November 7, 1996

Signature of Responsible Official [signature]

Title Vice-President