



July 7th, 2004

Dr. Lonnie Luther
Staff Chief, Generic Animal Drugs Team (HFV-104)
c/o Division of Dockets Management,
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852 USA

Dear Dr Luther

Re: Suitability Petition, Docket No. 2004P-0175

On April 14, 2004 a suitability petition was filed by Intervet Inc. (Docket No. 2004P-0175). The purpose of this letter is to provide a response to that suitability petition.

In the suitability petition Intervet Inc. requested permission to file an ANADA for a generic intravaginal insert for cattle that differed from the pioneer product (EAZI BREED™ CIDR® Cattle Insert; NADA 141-200) in terms of the strength of the active ingredient.

Based upon our experience with intravaginal inserts comprising progesterone and silicone, we would question whether bioequivalence studies alone would be sufficient to demonstrate that an intravaginal insert exhibited acceptable administration site safety and/or retention in the vagina of the cow. In addition we would question whether the insert described would be bioequivalent based upon the lower strength. We believe that it is not the total progesterone load that influences plasma levels, but the percentage weight per weight of progesterone in the inert silicone matrix that dictates whether a generic insert would be bioequivalent to an innovator product.

In our experience, in addition to the usual safety, efficacy and quality issues that apply to all drug products, two further aspects should be considered when evaluating an intravaginal insert. The first is whether the design of the insert (shape, dimensions, wing flexibility) causes any administration site safety related issues such as irritation, ulceration or erosion of the vaginal wall. The second is whether the design results in a high retention rate of the insert. Since the latter is directly related to the efficacy of the drug product, adequate studies to demonstrate acceptable retention rates should be performed.

Consequently we would conclude that blood levels alone would not demonstrate the safety and efficacy of the insert, because the design of the insert, as well as the formulation and drug load, would have a significant impact upon the products safety and efficacy.

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These points are expanded upon below.

Vaginal irritation

The degree of vaginal irritation and the extent of vaginal damage of an intravaginal insert is geometry dependant (shape and dimensions). Therefore, any change in the shape or size of a generic intravaginal product compared to the innovator could result in a different, and potentially unacceptable, administration site safety profile. For example, an insert that is designed smaller than the innovator may not be well tolerated because it may be able to move around in the vaginal cavity during the insertion period causing irritation or abrasions. Conversely, an insert that is designed larger than the innovator may exert excessive pressure on the vaginal wall resulting in ulceration or erosion of the vaginal mucosa. Alternatively an insert with a different shape to the innovator is likely to exhibit a different administration site safety profile e.g., the PRID is known to cause high vaginal irritation compared to the EAZI BREED™ CIDR® Cattle Insert, which is attributable to its shape.

Thus, the administration site safety of a generic intravaginal insert should be thoroughly assessed in order to ensure that the product exhibited acceptable administration safety. Such information would not be adequately determined through a one-off bioequivalence study.

Retention rate

To be efficacious an intravaginal insert must be present in the vagina of an animal throughout the entire treatment period, if it is not, then it would not be delivering the required amount of progesterone and therefore could not influence the hormone levels in the cow in order to synchronize estrus. Thus the retention rate of an intravaginal insert directly influences its efficacy.

The retention rate of an intravaginal insert is geometry dependant (shape and dimensions), and any change in the shape or size of a generic intravaginal product compared to the innovator could result in an unacceptable retention rate. For example, an insert that is designed smaller than the innovator may not be retained effectively since retention is dependant upon the slight pressure that the insert exerts on the vaginal wall. Therefore the smaller dimensions of the insert may not be sufficient to impel high retention rates. Conversely, an insert designed larger than the innovator may not be retained well due to too much pressure being exerted on the vaginal walls causing the cow to react to the inserts presence by contracting its vagina and expelling it. Alternatively an insert of the same size, but with a different shape to the innovator, may exhibit a very different retention rate profile to the innovator.

Thus, the retention rate of a generic intravaginal insert should be thoroughly assessed in order to ensure that the product exhibited acceptable retention rates. Such information would not be adequately determined through a one-off bioequivalence study.

Active concentration

Although, technically, it may be feasible to develop an intravaginal insert using silicone as the insert matrix that contained 1 g of progesterone that resulted in plasma levels that were potentially bioequivalent to the innovator product, this would depend entirely upon the relationship between the percentage weight per weight of progesterone in the insert and the surface area of the insert. Our studies have shown that it is not the total amount of progesterone in the insert that determines plasma progesterone levels, but the % w/w load. Further, our studies have shown that such a % w/w load must be combined with a certain surface area to achieve the desired plasma levels. Our studies would suggest that to demonstrate bioequivalence to the innovator EAZI BREED™ CIDR® Cattle Insert, a generic progesterone/silicone insert would have to possess at least a 7.5% w/w progesterone load in combination with a surface area of at least 75 cm².

Given this information we request that CVM deny the suitability petition.

Yours sincerely

A handwritten signature in black ink, appearing to read "Michael J Rathbone". The signature is fluid and cursive, with a large initial "M" and "R".

Michael J Rathbone
Director of Research



Please quote this Number if you have an enquiry.
GE988157169NZ

Customs Copy

1. From (Collection Address)

Account: 250119
Name: DEC (Manufacturing) NZ
Address: 558 Te Rapa Road
City: Hamilton
Province:
Postal Code: 2001
Country : New Zealand
Contact Name: Michele Jeffcote
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2. To (Receiver)

Name: Food & Drug Administration
Address: Generic Animal Drugs Team
5630 Fishers Lane
Room 1061 (HFA-305)
City: Rockville
Province: MD
Postal Code: 20852
Country : United States
Contact Name: Dr. Lonnie luther
Tel No: +1 301 827 8549
Customer Reference: Mike Rathbone

3. Goods

General Description: Documents

Total Packages: 1
Total Weight: 0.20 kgs
Total Volume:

4. Dutiable Shipment Details

Receiver's VAT/TVA/BTW/MWST:
Currency: New Zealand Dollar Value: 0

5. Services

Service: (15D) Global Express
Options: Priority

SENDER PAYS

Insurance: Insurance Currency: New Zealand Dollar 0

Senders Signature:



Date: 9/7/2004

6. Special Delivery Instructions

Special Delivery Instructions:

7. Invoice Receiver (Receiver's Account Number)

Received by TNT

Date: 09/07/04

Time: 11:20 am