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# QUICK MEMO

DATE: 9/19/97

ATTENTION: \_\_\_\_\_

TO  
Steve Sundlot  
FOA - cum  
7500 Standish Place - HFV-1  
Rockville, MD. 20855

SUBJECT  
Response to Request for Input  
on Minor Species / Minor Use Drugs.

On Sundlot -

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MESSAGE

Thanks for helping us with the FST problem - Here's the hard copy of our response. If there are any inaccuracies, please bring them to my attention. I'd like to be accurate on this. Our criticism is not to be taken personally and I do hope that some changes can be made to alleviate some or all of those problems. I'm sure our suggestion sounds "way out there", but it would result in alleviating the cited problems while keeping with the governmental mandate of a safe food supply -

SIGNED George Holzer

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To: FDA/CVM Veterinary Medicine Advisory Committee

From: George Holzer, FSH Committee, American Embryo Transfer Association

Subject: Good Manufacturing Practices, Minor Drug Approvals, and Import Alerts

Date: August 14, 1997

The embryo transfer industry in the US has experienced major adverse effects during the past few years that are directly related to the availability of a safe and effective product containing follicle stimulating hormone (FSH) which is an essential component of the embryo transfer procedure and vital to the embryo transfer industry. For many years an FDA-approved product containing FSH was available. The product, FSH-P was manufactured by Armour Laboratories and marketed by Schering. The following chronology traces the evolution of the FSH availability problem, identifies the factors involved, and finally suggests changes in the approval process that may ameliorate the present situation.

#### Chronology of Events-THE FSH\* PROBLEM

On Aug. 13, 1993, AUSA Inc., Tyler, TX obtains FDA approval for SuperOv for superovulation of cattle.

On Nov. 1, 1993 the FDA puts an import alert on FSH products, refusing entry to several hundred bottles of Ovagen (manufactured by ICP, Inc. Auckland, New Zealand) at the SFO airport customs office. This action invalidates an USDA import permit for Ovagen. AUSA takes credit for this import alert in its newsletter.

Spring 1995--FDA demands that Armour Labs bring their manufacturing lab up to GMP (Good Manufacturing Principles) standards, specifically that they develop a non-biological assay for FSH and another product used in human medicine. Armour extracts and sells FSH-P to Schering-Plough Pharmaceuticals. The cause of this action not known, though rumors implicate AUSA.

June 1995--Armour decides the cost of complying is too high. They cease supplying FSH-P to Schering. Schering announces to their customers that they are stopping the distribution of FSH-P, and sells ~18,000 doses in less than 6 hours.

November 1995--AUSA Inc., now the only remaining manufacturer of an approved FSH product, distributes nationwide two lot numbers of SuperOv that are found to be clinically ineffective (1ARB, 1ARC). This is a peak time of the embryo transfer year, and livestock owners and ET businesses suffer huge losses. More or

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less 70% of attempted donors fail to achieve multiple ovulation, and those that do have generally very poor production of viable embryos. The irony is that the AUSA laboratory is a GMP-qualified manufacturing site according to the FDA. A few ET practitioners file adverse drug reaction reports with the manufacturer and the FDA. Very soon five ET clinics are visited by FDA investigators (marshals) who are looking for "foreign" FSH products. Practitioners cease supplying adverse drug reaction reports.

January 1996--Adverse drug reaction reports are requested by FDA. Practitioners report verbally to the FDA because of fear of reprisal. FDA takes no action on the request for emergency importation of FSH to relieve the critical situation. FDA convenes an internal meeting about manufacturing problem at AUSA, Inc. Several independent labs analyze lots 1ARB and 1ARC in comparison with other batches of SuperOv and in comparison with other brands of FSH. Activity levels in these problem batches consistently reveals approximately 50% of normal activity, even though many different analytical techniques are used.

February 1996--American Embryo Transfer Association (AETA) asks for release of information about FDA meeting on FSH manufacturing problems, citing the FOI rules. (This information received approximately 10 months later).

March 1996--Ayerst Labs in Canada shuts down their bottling facility due to failure of FDA inspection for GMP standards. They bottle SuperOv for AUSA, Inc. Consequently there is no bottling facility for SuperOv for the US market. Curiously AUSA continues to supply SuperOv for many more months. Ayerst says they will no longer bottle for manufactures of US approved drugs due to these difficulties.

Spring 1996--Specialty ET distributors report that AUSA Inc. is not giving credit for the ineffective batches of SuperOv which the distributors have exchanged with dissatisfied customers. Distributors report that they will be selling their remaining stocks of "proven" SuperOv this summer and are not willing to supply any other batch lots. Other, less informed, distributors report they are selling the bad lots (1ARB, 1ARC) of SuperOv which AUSA, Inc. had shipped to them during the months of March, April, and May, 1996. Several angry ET business complain about disastrous results received with these problem batches which were shipped directly to them this spring by AUSA, Inc. These bad batches have also been shipped to South Africa and England this spring, and have failed to reliably stimulate cows on those continents. Apparently the problem is not seasonal or regional, and is not associated with other FSH products in use in those countries.

On May 14 and 16, 1996 the FDA inspects the AUSA manufacturing plant in Texas for GMP standards, presumably in response to the adverse reaction reports filed verbally by veterinarians. Fifteen deficiencies are found in the GMP standards, but the cause of the failure of the known bad batches is never discovered, and the owner of AUSA refuses to admit that he has a problem and instead blames the veterinarians, the weather, the season, and the cycle of the moon. Oddly enough, the only lab to produce FSH that actually had problems (batches 1ARB, 1ARC of SuperOv) is still in operation. As of midsummer 1997, it appears that no further action has been taken by the FDA on this matter.

Fall 1996--AUSA continues to sell SuperOv out of its Texas manufacturing lab, apparently now bottling the product on site. In October of '96, at the AETA meeting, AUSA announces that it is now producing equine FSH and ovine FSH and marketing those products without FDA approval, "because that's what everyone else is doing."

May of 1997- AUSA announces to customers trying to order SuperOv that it is no longer available on the market and probably will not be available in the future.

The committee of the AETA contacts the FDA and explains that there is no FSH available in the US. The FDA decides to do something. It is pointed out that the US has effectively been without FSH for about a year due to batch failures of SuperOv, and practitioners are curious as to what can be done now that couldn't be done earlier. The answer is that the FDA will be willing to take action in response to a manufacturer's action (removing the product from the market), but would not take action for reasons of product failure or the failing of a GMP inspection (related to FDA action). The FDA's solution was to cancel the "Import Alert", thereby allowing veterinarians to import FSH products and distributors to stock imported forms of FSH. Implied in this announcement, but not explicitly stated, is the understanding that veterinarians may use these FSH products in the extralable format (because foreign drugs do not have FDA approval). Also implied is the suggestion that veterinarians can import any drug provided that it is not listed on an "Import Alert". A relevant question is, "If an Import Alert had not been issued on this drug, could nothing have been done?"

Through out this entire period, ICP (New Zealand) has been working on approval of Ovagen by the FDA as a new animal drug for superovulation. After at least three years of work, that approval has never been obtained. Practitioners do not understand this delay since no tissue clearance studies are required for this class of drug.

Remember that the old FSH product (FSH-P) was approved in the 1950's, and served the industry relatively well for years. Schering has maintained that several improvements could have been made to the drug to improve its effectiveness. However, they explained that any attempt to modify the existing formula for manufacture would probably nullify the FDA approval and necessitate a completely new approval process which would cost millions of dollars. It now appears that they were correct. This same stricture prevents manufacturers from modernizing manufacturing facilities and moving to new labs. Any change in the old approval may cause the FDA to re-evacuate the approval.

The CVM is trying to do the right thing for veterinarians but the FDA's bureaucratic nature prevents it from streamlining the regulation process. The legal department has the final say on all matters. Consequently, ease of taking action (from a legal perspective) determines what action will be taken, not the characteristics of the situation from the veterinarian's or consumer's standpoint. The result is that the party which presents a realistic legal threat (a manufacturer) will receive action. Other, less organized groups (veterinarian and consumer groups) will be greeted with inaction. If action is wanted, one must be dealing with a mass media news event, or commence a lawsuit, or at least be a credible threat for a suit.

Summer 1997--AETA still hoping to somehow obtain multiple FSH products in this country. AETA still hoping to maintain the prescription authority to use reproductive drugs in accordance with PL 103-396 (AMDUCA). The FDA has promised a Compliance Policy Guideline covering the prescription use of reproductive drugs. These drugs do not fit neatly into to the therapeutic vs. production classification set up by the FDA. This rigid classification does not serve many drugs well, but is maintained by the FDA as a rigid either/or requirement. Many cattlemen are coming to the conclusion that the FDA is not only inadvertently responsible for the problem, they are unable or unwilling to help with a solution.

Because the FDA does not have sufficient resources to effectively do all the things that it is trying to do, I propose that its major emphasis in the approval process for minor use food animals should be to monitor public safety by concentrating on tissue clearance of drugs. **All other aspects**, such as determining dosage, determining use in specific species, toxicity studies, and laboratory GMP should be revised to encourage rather than deter approvals. The free market resulting from many manufacturers with approvals for competing animal drugs will efficiently shake out all but the effective ones, produced in manufacturing labs that have effective GMP. The small size of some veterinary markets should not restrict the number of drugs

available. Note that many foreign countries with animal industries far smaller than that of the US have many more approved animal drugs than this country. **The cost of approval by the FDA and compliance with arbitrary administrative requirements limits the number of drugs available.** This industry's experience has shown that the FDA bureaucracy, as presently constructed,

1. will remove effective drugs from the market (FSH-P),
2. allow poor quality drugs onto the market (SuperOv),
3. conduct haphazard arbitrary administrative inspections,
4. do nothing about GMP failures for some manufacturers,
5. respond to adverse reactions by sending investigators into veterinary clinics looking for imported drugs,
6. prevent improvements in efficacy and manufacturing efficiency via existing criteria, which require re-examination of the entire approval submission if changes are made in the originally approved product,
7. and prevent effective drugs (new and imported) from reaching the US market.
8. prevent new and innovative uses for an approved drug for novel disease conditions and management conditions which are distinct from the indication on the label.

The current cost of FDA approval places a monopolistic condition around any approved drug and applies all of the ugly attributes of any monopoly.

The AETA believes it is time for CVM/FDA to restructure its approval process for minor use animal drugs to emphasize animal and human safety, establish GMP criteria that will allow small entrepreneurial companies to enter the animal drug market, and realistically reorder its other priorities for approval of minor use drugs.

Thank you for the opportunity to comment on these important issues.