

SECTION IV
ADVERSE DRUG REACTION
REPORTING SYSTEMS

FOOD AND DRUG ADMINISTRATION / CENTER FOR VETERINARY MEDICINE ADVERSE DRUG EXPERIENCE REPORTING - PHARMACOVIGILANCE FOR ANIMAL DRUGS

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An Overview and Update

My purpose this morning is to provide an introduction to CVM's adverse drug reaction monitoring program for those who are not familiar with it, and to provide an update for those of you who have previously been exposed to or participated in the program in some way. I will organize my talk into four main subtopics: Scientific and regulatory basis for the program, Process description and update, Outcomes, Areas for improvement.

Scientific And Regulatory Basis For The Program

What are the functions of CVM's pharmacovigilance program, and why is a pharmacovigilance program needed. First let's define what we mean by pharmacovigilance: Pharmacovigilance refers to the generation, collection, maintenance, and evaluation of spontaneous adverse drug experience information. This is a more narrow definition than some have used, but I want to distinguish it as an activity and a process, rather than as a discipline. For comparison, pharmacoepidemiology is the study of the use and effects (typically but not always adverse effects) of drugs in large numbers of subjects.

Science

The two primary functions of our pharmacovigilance program are (1) to gather information to detect unreported or unvalidated effects or clinical manifestations of drugs after they are marketed and introduced to large populations of animals and (2) to monitor for unsafe product, use practices, and unsafe products.

A Third Function, Related To Extralabel Use Will, No Doubt, Become Increasingly Important.

The first function is an important, but often overlooked contribution to product safety. In spite of the highest standards for safety and effectiveness that exist for FDA approval, not everything is known about a drug when it is first marketed. Due to the limited size and controlled nature of premarketing clinical trials, only the most common adverse events will be observed and included in product labeling at the time of FDA approval. An accurate safety profile emerges only after a product is marketed and the number and spectrum of animals receiving the drug increases. Therefore, information on adverse effects that occur at a consistent but low rate, or more frequently but primarily in a breed or population that was not included in investigational studies, would not be available from preapproval clinical trials or target animal safety testing. The number and variety of animals exposed during the investigational process is simply inadequate to detect anything beyond frequently occurring adverse events.

To illustrate what I mean let's look at the Rule of Three: This rule tells us that studies containing 300 subjects which have no cases of adverse events reported are required, in order to make the negative assumption that any adverse events that might occur would occur with a risk of $<1/100$. Similarly, for assumptions of risk of $<1/1,000$, and $<1/10,000$, studies of 3,000 and 30,000 subjects, respectively, would be needed. Clearly, studies of this magnitude are beyond the scope of the approval process for most animal products. When untested variables such as breed, sex and age differences in response to drugs are layered onto the already limited number of animals tested in the preapproval clinical trials, it

becomes very clear that the information on adverse experiences gathered by pharmacovigilance during the first one or two years of product marketing is critical to developing an adequate safety profile for a newly marketed product (Fig. 1).

The value of the second function - detecting unsafe products and product use practices is perhaps more intuitively obvious, but on the other hand it is more difficult for the veterinary profession and industry to deal with constructively. This is because the examples we cite as the basis of need are examples of failure. By that I mean what we would like to measure and cite are examples of success. Thousands of safe and effective products are marketed with no need for regulatory intervention. In fact, what we typically cite are a few infrequently occurring examples of unsafe practices or unsafe products. The value of these examples is that they remind us that, despite a comprehensive preapproval information gathering process, a rigorous requirement for products to be manufactured under Good Manufacturing Practices, and the best intentions of veterinarians, distributors, manufacturers and FDA that all products be safe and effective, occasionally bad things happen. Its important and attention grabbing to cite these examples of unsafe products or practices but its admittedly more difficult to measure the safeness that occurs due to the rapid response, or perhaps as important, the deterrent effect of an active pharmacovigilance program. Clearly many sponsors currently conduct their business in a responsible manner. What is not clear is what would happen if the pharmacovigilance program were to disappear or be seriously compromised. Would industry have the same level of product stewardship? Would the Agency be able to respond as effectively? At this point we can state that these are rare, but potentially catastrophic events that industry and CVM must both guard against, and maintain a highly effective response capability when these events occur.

Extra Label Use Safety Information

The third factor is: Adverse Experiences Arising in Association with Extra-label Use.

A situation that is encountered frequently in veterinary medicine - a product used extra-labelly in a species or by a route for which it is not approved and for which limited clinical data is available, would obviously also lead to instances where information on even relatively common potential adverse effects would likely not be available from clinical trials or target animal safety testing. For instance, in a recent study of our adverse reaction data base, approximately 50% of the reported adverse reactions were found to be associated with extra-label use. This does not mean that extra-label use leads to adverse reactions; what it does mean is that for up to 50% of the adverse reactions in our data base the drug manufacturer is under no obligation, and, in fact, may be prohibited from initially placing that adverse reaction information on the product label during the approval process. However, following approval, based on pharmacovigilance obtained information, we have allowed and will continue to allow, or even require manufacturers to include this type of safety information on the product label.

Regulations

Next let's briefly review the regulatory basis for our pharmacovigilance program. Section 512(l) of the FDCA requires maintaining records and making appropriate reports of drug experience. These requirements are implemented under 21 CFR part 510, New Animal Drugs, subpart D. Records and Reports. Under this regulation, Sponsors of approved new animal drugs are responsible for establishing and maintaining records concerning experiences with their drugs and for submitting reports of those experiences to CVM. This means that, by law, reporting of adverse events is required from drug manufacturers. Among the ADR data which must be submitted are expected adverse reactions (those listed on the label), unexpected adverse reactions (those not on the label), and unexpected incidence of adverse reactions or unexpected severity of adverse reactions. Expected adverse reactions occurring at expected frequencies may be submitted as part of the sponsor's periodic Drug Experience Report, generally annually, on the anniversary date of the product approval. All other adverse events must be investigated by the sponsor and reported within 15 working days to the Center. These adverse reactions are reported on an FDA form 1932 by the sponsor. Serious product defects such as mislabeling or mix-ups must be reported immediately.

Process Description and Update

One of the primary goals of our pharmacovigilance program is to assess causality. To answer the question: Did the drug produce the adverse effect? Causality assessment is a multi-faceted process. Figure 2 shows the various steps of the ADE report process. An assessment of the ADE report occurs at several points indicated by asterisks in this flow-chart: The veterinarian or owner, and the sponsor, who must investigate the report, will assess causality. However, I want to concentrate on the CVM activities, Veterinary Medical Officer assessment using an algorithm, as well as the Monitored Adverse Reaction Committee, in my discussion.

The two elements of causality assessment at CVM are the Monitored Adverse Reaction Committee, or MARC, and the algorithm used to assess each adverse experience report by CVM VMO's.

The assessment of a potential cause-effect relationship is the purpose behind a pharmacovigilance program. Ultimately, the value of any regulatory action taken, whether it is addition of an adverse reaction section, or precaution statement, or other label change, change in dosage formulation, alteration in manufacturing or even product withdrawal is based on the existence of a real cause-effect relationship between the products use and the adverse experience. One important tool for establishing that relationship is an objective professional assessment of all ADR reports. In order to achieve this objective assessment CVM uses an algorithm. The purpose of using the algorithm is to assess whether an observed adverse event is actually an ADR, by utilization of standardized criteria. These criteria enable ranking the probability that the drug caused the event. This method is designed to produce accurate and consistent decisions and to eliminate arbitrary and subjective judgements as much as possible.

The algorithm we use is derived from Kramer et al, JAMA, 8/17/1979. (An algorithm for the operational assessment of adverse drug reactions.) I will describe in some detail the use of this algorithm in assessing adverse drug reactions; however, I want to state that the algorithm is a flag and an assessment tool for ultimately reaching the correct cause-effect conclusion and determining the appropriate regulatory action. Algorithm scores do not, by themselves, determine whether an adverse reaction will be included on the label. The key organizational element in the assessment process is the Monitored Adverse Reaction Committee and I would like to first describe the functions of this committee.

The MARC is a Division of Surveillance committee. The committee charter states that MARC as a functioning body will:

1. Establish criteria for, and select MAR products for evaluation.
2. Prioritize these products to facilitate a focused, efficient, in-depth, review of their relationship with the reported adverse drug reactions.
3. Evaluate the findings of the in-depth review.
4. Make recommendations for appropriate regulatory actions.

The membership of the committee consists of the division director and branch chiefs, ADR program manager, database manager, and executive secretary, but can be expanded to include needed expertise as appropriate. Recently we have been requesting participation from the appropriate product division in NADE. Thus the MARC provides a formal mechanism for consideration of information on adverse reactions and reaching appropriate decisions to ensure product safety.

Let me now describe the algorithm process used by the center to evaluate each report of an adverse experience.

The division uses a standardized set of medical terms to describe adverse events. This set of standardized terms, called clinical manifestations (CM's), is the key to maintaining a useful database. All clinical ADE reports are summarized using these standard terms. The CM's are then evaluated using our algorithm.

The algorithm consists of six factors of decision strategy with a scoring system incorporated into each factor. These factors and the scoring system are as follows:

a) Previous experience with the product:

If the CM is recognized to occur in a given species at the dosage received, a score of +1 is given. The recognition of inherent drug toxicity can be gathered from various sources including CVM approved package inserts, text books and annual summaries of ADRs distributed by CVM. A zero score is given when a CM is not generally recognized or post-marketing clinical experience with the drug is limited.

A score of negative one is given when it is unlikely that the reported CM is linked with the suspect drug on the basis of the current knowledge and/or substantial accumulated post-marketing clinical experience with the drug.

b) Alternative Etiologic Candidates:

A score of +2 is given when the CM is not associated with a pre-existing condition including its exacerbation, recurrence or complications, concomitant medical problems, concurrent drug administrations or associated drug interactions; but is causally related to the suspect drug. A zero score is assigned when the causality of the CM can neither be unequivocally linked to alternative etiologic factors described above nor to the subject drug. A score of -1 is assigned when any of the aforementioned alternate factors are responsible for CM.

c) Timing of Events:

The temporal relationship between the administration of the drug and onset of the CM determines the scoring under this factor.

A score of +1 is given if pharmacokinetics parameters (biological half life, plasma/serum concentrations, depletion kinetics and other parameters) support a relationship between the CM and the suspect drug.

A zero score is assigned when such a link between the CM and the suspect drug cannot be established.

A score of -2 is assigned when the temporal relationship between the CM and drug administration cannot be established on the basis of pharmacokinetics parameters.

d) Evidence of Overdose

A score of +1 is given when the CM is dose related and the report provides evidence of overdose.

A score of zero should be assigned when the aforementioned dose related causal relationship cannot be established or the CM represents idiosyncratic reaction.

e) Dechallenge

A score of +1 is given, in the event CM is diminished upon discontinuation of the drug or after administration of a specific antidote. In addition, if the sum total of the scores of the first four determinants is equal to or exceeds +3 and CM diminishes by dose reduction, a score of +1 should be given. The summation score of +3 or more of the first four factors would mean that the CM is a recognized manifestation following drug administration and has causal and temporal relationships with the subject drug.

A score of +0* is assigned when CM did not diminish by dose-reduction, was transient or episodic, responded to non-specific antidote or was inappropriate or difficult to assess.

A score of -1 is given, when CM has no causal relationship with the discontinuation of the drug or reduction in its dose. The CM continues even after discontinuation of the drug or improves without dechallenge.

f) Rechallenge

When CM unequivocally recurs or is exacerbated on rechallenge, a score +1 is assigned; and -1 is given when no exacerbation or recurrence of the CM results even after rechallenge with the drug. A score of +0 is given when no rechallenge was attempted or rechallenge assessment was obscured by various factors including the drug.

The CM is definitely related to the suspect drug when sum total of the score is +6 to +7; probably drug related with score of +3 to +5; possibly drug related when the score is between +0 to +2. The relationship between CM and the suspect drug is remote when the total score is negative (-1 to -6). (Fig. 3).

A score of -7 is assigned when no conclusion could be arrived as to the association of the CM and the suspect drug. When the lack of information precludes judgmental decision as to the causal relationship of the CM with the drug, a score of -8 is provided.

When the product complaint did not involve the animal, for instance, the drug was not administered to the animal, a score of -9 is assigned.

The ineffectiveness of the drug to produce the desired effects listed under indications of the package insert is also rated as definitely (+6), probably (+3), possibly (+0 to +1), or remotely (-1), drug related. This is a judgmental call which is not subjected to the rigorous six factor analyses since the drug is approved after extensive efficacy trials.

As a result of this approach the center has accumulated over 12,000 reports in our database. Each report is comprised of identifier information such as product and species, and standardized CM's which have been categorized with respect to causal-relationship to the product.

Every ADE report received by the center is evaluated by a veterinarian in the Division of Surveillance using the algorithm. Causality assessments and ultimately regulatory actions flow through the MARC. By way of comparison with other FDA Centers, human product reports are typically filed with the agency in duplicate, the product division does a subjective expert assessment using one report, while a separate epidemiology division captures report descriptive data in their ADE database. Teams are formed to assess causality. There is also a MARC process. The center for human drugs typically receives in excess of 150,000 reports annually. This table gives an overview of our annual ADE workload. The increase over the last 3 years can be largely attributed to new products - particularly Posilac®. (Fig. 4).

Outcomes and Regulatory Products

Let me briefly outline the options for our use in response to voluntary reports from veterinarians to the drug manufacturer. We can issue warning letters, require label changes, require the manufacturer to conduct postmarketing studies, require a formula change or initiate action to withdraw approval. We very seldom require a recall, undertake a seizure, or initiate an injunction. We use these enforcement tools carefully and only after rejection of less resource costly alternatives. What I want to do is provide you three recent examples of adverse drug reactions that illustrate the effectiveness of our pharmacovigilance program: (1) to detect unreported or unvalidated effects or clinical manifestations of drugs after they are marketed, (2) to monitor for unsafe product use practices, and (3) identify unsafe products. I think you will agree that this is an effective program that delivers a large beneficial outcome for minimal input.

Accomplishments

- A. To detect unreported or unvalidated effects or clinical manifestations of drugs after they are marketed

Otomax was approved in 1993 for treatment of canine otitis externa. It is a combination drug product containing gentamicin sulfate, betamethasone valerate, and clotrimazole. During clinical trials there were no reports of hearing loss. The possibility of hearing dysfunction was included as a standard statement in the precautions section of the package insert, although the location was not prominent. Following approval ADE's were received that suggested that the product may be associated with deafness in some dogs. The follow-up investigations suggested that the deafness is usually temporary if the ear is flushed when the problem is first noted and use of the product is discontinued. There was a very clear reporting pattern for the ADE reports. Most of the reports were assessed as possibly or probably drug related using our algorithm. In July of 1994 we requested that the sponsor submit a supplemental New Drug Application to add a label warning of deafness. The letter recommended specific language and label location for the change. The goal of this change is to heighten the awareness of prescribing veterinarians of the possibility that the problem may occur and to ensure appropriate therapy if needed. The sponsor responded with a letter of agreement in late 1994.

- B. Unsafe product use practice involving ELU

During late 1992 we received numerous reports of deaths in feedlot cattle associated with intravenous administration of spectinomycin, primarily from the product manufacturer. This particular product was an oral product that was being compounded by veterinarians into an intravenous product. Despite reports that cattle are resistant, the signs reported for these cattle were consistent with endotoxin. The sponsor voluntarily approached the CVM and submitted a Dear Doctor letter warning of the dangers of compounding their oral spectinomycin product into an intravenous product. CVM agreed to the immediate release of this letter. Prompted by CVM, the sponsor's further investigation showed high levels of endotoxin in their product. This should not be surprising since endotoxin is generally not a problem in oral products and no endotoxin release specifications are required for oral products. The sponsor subsequently voluntarily instituted endotoxin release specification for their product. We don't know if the Dear Doctor letter, the newly instituted endotoxin release specifications, or perhaps a combination of both were responsible - but we do know that shortly thereafter the number of reports of adverse reactions associated with this product dropped to nearly zero.

- C. Monitoring for Unsafe Products

In November 13, 1995, CVM received a FAX from the Nebraska State Department of Agriculture. Two herds of cattle treated with Warbex (Famphur) pour-on for cattle showed clinical signs of organophosphate toxicity. Several cattle deaths were reported. Warbex is an OTC organophosphate approved for control of cattle grubs and reduction of lice infestations. The

product is manufactured under contract by PM Resources at a facility in St. Louis, Missouri. The product used to treat both herds had come from the same store and was from one lot number. Lot number 950658 was removed from shelves in the feed store and held for pickup by sponsor. The lot had been sold to one chain of stores. The stores were all linked by E-mail. This lot was removed from all store shelves the following day. Attending veterinarians submitted necropsy samples to the state animal disease diagnostic lab. Depressed brain cholinesterase levels consistent with organophosphate toxicity were found. They also phoned the drug sponsor. There was some involvement of the state veterinarian. The state notified the FDA Kansas City District Office. CVM reviewed the ADE database and determined that an average of 2 or 3 reports per year was common for Warbex. CVM requested immediate submission of Adverse Drug Experience reports providing the details of these and any other complaints.

There was a barrage of E-mail and phone communication during the first few days prior to receiving an official ADE report from the sponsor. The Division of Surveillance began a telephone dialog with the sponsor. Telephone contact between the Division of Surveillance and the sponsor continued to occur on a daily, or alternate day basis, for a period of approximately two weeks.

On November 20, the animal diagnostic laboratory at Michigan State University reported that High Pressure Liquid Chromatography analysis of a Warbex sample from lot 950658 revealed a contaminant later identified as isazophos. The sponsor requested immediate testing of retained samples of Warbex for isazophos contamination. The sample had been submitted by the veterinarian treating one of the affected herds. The container had been opened and used, so there was some question about where the contamination had occurred.

FDA sent a field investigator to pick up samples at the store. Field investigators were sent to the farms reporting the initial problems and to the manufacturing facility. FDA labs analyzed samples collected by the investigators. The field investigator who visited the two farms that first reported problems concluded that the contamination did not occur on the farms. The investigators who inspected the manufacturing site reported that, although isazophos was present in the facility, their preliminary conclusion was that the contamination occurred elsewhere.

During the course of the recall, analytical work was conducted by: the manufacturer, two state diagnostic labs, two FDA labs, and a private contractor working for the drug sponsor.

The sponsor began a voluntary product recall of lot 950658 on November 21. At that time there had been six ADE reports submitted with a total of 800 animals treated, 163 showed signs of toxicity, and 71 died. The isazophos product is diluted approximately 100:1 with water prior to use. Clearly the undiluted product would be more potent than Warbex.

After discussions with CVM the sponsor published newspaper advertisements and broadcast radio and television warnings advising purchasers of Warbex lot 950658 to return the product to the point of purchase. There was some delay in getting returned product shipped back for lab analysis because it requires special handling as hazardous materials.

In addition to the animal safety problem, the situation presented a human food safety risk and potential toxicity to humans handling the product. Isazophos is a turf insecticide licensed by the EPA. There is no food animal withdrawal time because the product is not for use on animals. Livestock producers were advised not to sell or slaughter any cattle treated with this lot until a tissue withdrawal time could be calculated. CVM began a dialog with USDA FSIS to ensure that cattle treated from this lot were not marketed. CVM Division of Chemistry calculated a withholding time for affected cattle.

On November 27 lab analysis confirmed the presence of isazophos in retained samples of lot number 950658. Shortly thereafter, PM resources contacted the FDA and reported that an employee had admitted using a transfer line used to fill isazophos containers without prior

flushing to fill contaminated Warbex containers. The contamination was believed to be limited to lot number 950658. Furthermore, high levels of contamination are believed to be limited to a relatively few containers filled at the beginning of production of this lot.

As of December 27, 1995, CVM had received 39 ADE reports for Warbex. A total of 5541 cattle were treated, 423 reacted and 135 died. Approximately 50% of the animals affected were treated with the recalled lot. The other half were treated with one of eighteen other lots of the product.

There have been no recent reports of ADE's with this product. Most of lot 950658 has been accounted for. The sponsor has agreed to analysis of the recalled material to determine the potential for the remaining gallons to contain high levels of isazophos. Only a few gallons of Warbex are believed to be significantly contaminated. A high level of isazophos in the commingled returned material would suggest that most of the highly contaminated cans have been returned.

These examples of catastrophic events serve as reminders of the importance of a pharmacovigilance program, cooperation between industry, practicing veterinarians, and state and federal agencies. They also serve as reminders of the rare but necessary need for rapid communication and decisive action by industry and government. I am pleased to play a role in the pharmacovigilance program and welcome the greater involvement of practitioners and academicians in helping to achieve animal drug labels which are as accurate as possible in reflecting expectations, both good and bad, under the actual conditions of product use.

Opportunities for Improvement

I would like now to move to my final subtopic - Opportunities for Improvement. A pharmacovigilance program for animal health products is comprised of a partnership of three elements: industry, veterinarians and their clients, and regulatory agencies. If one member of this partnership fails, the program will fail. We must all contribute. Additionally, in order to carry out a robust and vital pharmacovigilance program we need the strengthening contributions of organizations like AVMA, the National Animal Poison Control Center and USP. Without their support the program will be weak and ineffectual. In short, we must all work together and contribute our resources to make the program work. I would like to suggest some things that each group could do to strengthen the pharmacovigilance program.

First, what can the FDA do?

1. Simplify the reporting form and provide widely disseminated instructions for completing the form.
2. Work with other agencies to reduce the confusion about which agency to report a product defect/or adverse reaction.
3. Provide easy and/or frequent access to ADR information.
4. Provide materials for use in teaching pharmacovigilance concepts in veterinary schools.
5. Maintain confidentiality of reporters.

What can veterinarians do? Report!

The initial requirement in our pharmacovigilance process is for a veterinarian or animal owner to be sufficiently concerned to contact the sponsor, USP's Veterinarian's Reporting program or CVM or other regulatory agency directly to report an adverse experience with a product. Without this first step there can be no Dear Doctor letters advising of product problems, no revision of adverse reaction or contraindication sections on labels, or no product defect-related recalls. Of all the elements in the pharmacovigilance process this participation is the most critical.

What can industry do?

Be a good steward. Avoid filtering. All reports regardless of whether or not it is attributable to a drug should be investigated and submitted to CVM.

What can educators at Veterinary Colleges and other organizations do? Veterinarians and veterinary students must be made aware of the benefits of the program, how to participate, and why it is important.

1. Emphasize pharmacovigilance in CE programs at professional meetings.
2. Include pharmacovigilance in Veterinary College curriculums.
3. Include pharmacovigilance as part of accreditation for Veterinary colleges and veterinary hospitals.
4. Include regular pharmacovigilance material in journals.

This concludes my remarks. I hope I've at least stimulated your thinking in this area and begun the process whereby we can change the thinking of the veterinary profession in this area in a way that will ultimately result in enhanced safety and effectiveness of veterinary products - a goal we all share.

Abbreviations

CVM = Center for Veterinary Medicine
FDCA = Federal Drug and Cosmetics Act
ADE = adverse drug experience
ADR = adverse drug reaction
VMO = veterinary medical officer
MARC = Monitored Adverse Reaction Committee
MAR = monitored adverse reaction
JAMA = Journal of the American Medical Association
NADE = new animal drug evaluation
CM = clinical manifestations
ELU = extra-label use
FIFS = Food Safety Inspection Service

*******ALGORITHM TABLE*******

<u>CODE</u>	<u>DEFINITION</u>
+6 TO +7	DEFINITELY DRUG RELATED
+3 TO +5	PROBABLY DRUG RELATED
+0 TO +2	POSSIBLY DRUG RELATED
-1 TO -6	REMOTELY DRUG RELATED
-7	NO CONCLUSION
-8	INFORMATION LACKING
-9	NOT APPLICABLE
+6	INEFFECTIVENESS--DEFINITELY DRUG ASSOCIATED
+3	INEFFECTIVENESS--PROBABLY DRUG ASSOCIATED
+0 TO +1	INEFFECTIVENESS--POSSIBLY DRUG ASSOCIATED
-1	INEFFECTIVENESS--REMOTELY DRUG ASSOCIATED

(Fig. 3)

CVM ADR WORKLOAD SUMMARY BY YEAR

<u>FY</u>	<u>REPORTS</u>	<u>ANIMALS AFFECTED</u>
95	2,730	57,430
94	1,690	105,000
93	1,380	28,900
92	1,500	14,400
91	940	16,800
90	1,230	52,000

TOTAL REPORT INVENTORY FOR 1987 - 95

>12,000 REPORTS

(Fig. 4)

THE USP VETERINARY PRACTITIONERS' REPORTING PROGRAM

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Background: The United States Pharmacopeia

The United States Pharmacopeia (USP) is a private, non-profit, organization established in 1820 by eleven physicians who recognized the need for drug standardization across the regions of the United States. USP is now composed of more than 1,000 volunteer experts from around the world who serve on its subcommittees and advisory panels as well as a core staff of more than 240 individuals.

Standards Development: USP's primary mission is to set standards for drugs and related technologies. Most commonly recognized are standards for determining the identity, strength, quality, and purity of the articles and specifications for packaging and labeling. The standards set by USP are recognized in the Federal Food, Drug and Cosmetic Act and, as such, are enforceable by the Food and Drug Administration (FDA). Currently, the USP-NF book of standards lists standards for over 3200 products, including more than 100 products used in veterinary medicine.

Information Development: In an effort to enhance the safe, effective use of medications, the USP began publishing drug information for practitioners, consumers, and patients in 1980. This publication, USP DI, is recognized by the US Congress as an "official compendium" for use by state Medicaid agencies and for information on medically accepted unlabeled uses of medications. The database of this drug information system covers practically all medications available for use in human beings in the United States and Canada, and currently includes monographs on nearly 90 drugs for animal use.

Reporting Programs: Supporting the work in the standards and information areas, USP also operates, since 1971, the USP Practitioners' Reporting Networks (USP PRNs). The network, which was initiated in cooperation with the FDA, provides a means by which health professionals and others may identify problems with the quality, performance, and safe use of medical products once they are available in the marketplace. This network is comprised of three reporting programs for "human" products and one program, the Veterinary Practitioners' Reporting Program, dedicated to processing veterinary reports.

The Veterinary Practitioners' Reporting Program was launched in September 1994 in cooperation with the American Veterinary Medical Association. This nationwide program collects reports from veterinarians and their staffs regarding the quality, labeling, packaging, and safe use of drugs, vaccines, pesticides and other medical products related to veterinary medicine. Reports are submitted to USP either by mail, fax or by phone and on-line reporting is expected to be available in the near future.

Evolution of the Concept

Until 1990, USP had focused its standards-setting and information efforts primarily on **human** drugs, and a limited number of related medical devices. Although a Veterinary Medicine Advisory Panel, composed of volunteer experts from industry, government, and veterinary practice throughout the U.S. was appointed in 1980, and a few veterinary monographs had been included in subsequent publications of the DI, it was not until 1990 that the USP's membership formally committed the organization to creating standards and information for **animal** drugs.

As part of its official functions, the Veterinary Medicine Advisory Panel periodically reviewed sporadic reports received by USP's reporting programs on products used in veterinary medicine. These reports were accepted through the "human" reporting program because no specific veterinary program existed at

that time. Reports were generally submitted by pharmacists working in the veterinary field who were already familiar with USP. One of USP's panelists, the Deputy Director of the Food and Drug Administration Center for Veterinary Medicine (FDA CVM), was pleased to learn that all reports submitted to USP were being shared with the FDA and the product manufacturer for follow-up and any necessary action. In June of 1992, the USP Advisory Panel expressed its interest in seeing USP bolster reporting mechanisms for animal drugs, and solicit reports more aggressively for the benefit of the veterinary profession, regulators, and USP standards and information panels. Toward that goal, over the next 18 months, USP worked to secure the commitment of the American Veterinary Medical Association to encourage and support the implementation of the Veterinary Practitioners' Reporting Program. That support was received in November of 1993.

Evolution of the Program

The first step was to develop a reporting form as a data collection instrument. A form was drafted using the template of the FDA form 1932 as its basis. The form was then distributed for comment to the AVMA Council on Biologics and Therapeutics and its Drug Advisory Committee, as well as the FDA CVM, and the USP Veterinary Medicine Advisory Panel. Comments were incorporated and the reporting form was printed for distribution. The launch of the Veterinary Practitioners' Reporting Program was announced in the September 1994 issue of the AVMA Journal, followed by a mailing to AVMA membership in October of 1994. Almost immediately, reports were received by mail and through the program's 24-hour toll-free phone line. A copy of each report was routinely forwarded to the appropriate regulatory agency (FDA CVM, USDA APHIS, EPA) and to the respective manufacturers of the products involved.

As expected, USP received many inquiries from the industry in response to these reports - questions centered around the reporting process in general and the manufacturer's responsibility to respond to the reports. Fortunately, in February of 1995, USP was invited to participate in the Animal Health Institute's (AHI) Animal Drug Section Meeting on Adverse Reactions which was designed to help the industry better understand the workings of the reporting program as well as its interface with existing regulatory programs. Its panel included representatives from USP, FDA and USDA. The dialog with the industry during this meeting was very productive and resulted in several changes in and improvements to the program. Below are four of the most important ones:

Questions & Answers Document: Based on the many questions and concerns expressed by the industry at the AHI meeting, USP, in cooperation with the USDA, FDA, AVMA and AHI, compiled a pamphlet of questions and answers which addresses issues such as the possibility for duplication of reports; the interface of existing regulatory reporting programs with the USP Program; and the handling of confidential and anonymous reports received through the program. The pamphlet is included the packet of information distributed at the AAVPT meeting. Additional copies may be requested through USP PRN.

Manufacturer Contact Persons: Using an AHI-provided member mailing list, USP provided AHI members with information on the program and asked each company to name a contact person responsible for receiving reports. In addition to receiving routine reports by mail, the contact person is alerted immediately by fax or phone if serious health hazards or deaths are reported. By appointing such a contact person, the firm's response and follow-up with the reporter may be expedited.

USP Staffing: When the program was initiated, the same pharmacists and nurses who handled the "human" reports also processed the veterinary reports. In July of 1995, a full-time USP staff veterinarian became available to accept telephone reports and review all written reports received through the program.

Reporting Form: Although a great deal of effort was put into the original draft of the reporting form, some areas for improvement were recognized by USP staff, the industry, and reporting veterinarians alike. As a result, the form underwent complete revision in April of 1996, with input from representatives of the AHI, AVMA, FDA CVM, USDA APHIS, EPA, and veterinary practitioners. The current version has several notable improvements which bring us closer to our goal of collecting essential information while not overly burdening the practitioner.

Interfacing with Other Programs

Since USP's Veterinary Practitioners' Reporting program shares 100% of its reports with regulators and industry alike, it functions to augment rather than compete with other programs by facilitating practitioner reporting. In fact, 65 of the 100 adverse reactions reported to USDA's Veterinary Biologics Field Operations in 1995 were received via USP's program. It should be clearly stated that USP never discourages reporters from directly contacting manufacturers and regulatory agencies when a problem occurs and, by providing reporter information in 99% of the cases, makes it possible for industry and regulators to gather more comprehensive information directly from reporters if necessary.

The following unique characteristics of the program make it attractive to the practitioner and facilitate reporting. These characteristics also assure that the program offers features unavailable through other programs and that it is indeed filling a need.

"One-stop shopping": USP Veterinary Practitioners' Reporting Program provides the practitioner with a means to alert the manufacturer, appropriate regulatory agency, and the AVMA by making only one phone call or completing only one form (which has been developed with the concerns of all parties in mind). Many practitioners are unfamiliar with the responsible regulating agencies and which products are within the respective jurisdictions. The USP system makes it simple to report and assures the reporter that his or her information will be forwarded to all involved parties. Reports regarding problems with any animal healthcare product used in any animal species are accepted.

USP is a neutral, unbiased third-party: Many practitioners feel uncomfortable contacting representatives of a government agency or manufacturer, and like the idea of reporting to an impartial party that accepts the information and conveys it appropriately. Some practitioners have expressed the opinion that their concerns may be taken more seriously by the manufacturer and/or the regulatory agency if a third-party transmits them. Also, while we do not encourage it, anonymous reports are accepted. In such cases, USP will act as an intermediary should any other party wish to receive more information from the reporter. Less than 1% of reports are submitted anonymously and reporters are advised that this choice may limit follow-up investigation of the situation.

USP is a private organization: One reason representatives of FDA CVM have given enthusiastic support to the program and do not feel it is duplicative of the Center's own adverse event reporting program is that it is not a government-run program. As such, it is not subject to government funding issues and enjoys greater control and flexibility in allowing its evolution in response to issues as they arise. The many improvements made to the program in response to concerns of industry and the timely, cooperative revision of the original reporting form provide evidence of this advantage.

USP offers a toll-free number for use by practitioners nationwide: An established toll free telephone line allows for ease in reporting and the ability for practitioners to address issues directly with a USP staff veterinarian. The toll-free number operates 24 hours a day to accept reports. The line is staffed by a veterinarian between the hours of 9 a.m. - 3 p.m. ET.

Future of the Veterinary Practitioners' Reporting Program

Pre-marketing federal regulations are in place which help assure that products entering the veterinary market have been proven safe and effective in a relatively small number of animals. However, problems encountered once the product becomes commercially available and is in wide-spread use can only be recognized and acted upon if practitioners report them. Mechanisms for reporting have been available to health care providers in the human field for 25 years; however, organized reporting is a relatively new concept in veterinary medicine. The USP Veterinary Practitioners' Reporting Program is responding to a need in the veterinary community and in doing so, is gradually assuming the form which best serves veterinary practitioners, regulators, and the animal health care industry alike. With the continued, cooperative efforts among individuals, organizations, and companies dedicated to animal health, the

Veterinary Practitioners' Reporting Program will provide a means by which veterinary practitioners can take an active role in creating a safer environment in which to practice veterinary medicine.

EXPERIENCE WITH AN INDUSTRY-BASED ADVERSE DRUG EXPERIENCE RECORDING SYSTEM FOR POSILAC®¹

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INTRODUCTION

POSILAC® bovine somatotropin was approved for commercial sale based on data from controlled studies. Upon FDA approval of any drug, a measure of the commercial incidence of health-related items is required by FDA. Those data provide further information under commercial conditions on animal safety and efficacy. As for any product, submissions for POSILAC® include a reporting system for adverse drug experiences (ADE). An ADE is defined as "any side effect, injury, toxicity or sensitivity reaction (or failure to perform as expected) associated with the use of an animal drug, whether or not determined to be attributable to the drug" (Oeller, 1995).

Protiva's system for collecting adverse drug experiences with POSILAC® was unique because it proactively sought out and recorded farmers' experiences whether or not they were thought to be related to product use. After a customer placed their first order for POSILAC®, Protiva followed up with every client several times after they had received the product by placing outbound telephone calls from our Customer Service Center. In addition, each time the customer called to order a product or ask for information, their experience with POSILAC® was queried. Thus, we are confident that we have been able to directly contact and report the experiences of virtually all commercial dairies that used POSILAC®.

METHODS

Protiva's POSILAC® Inquiry/Complaint System

All POSILAC® ADEs were processed and submitted through Protiva's Regulatory Affairs office in St. Louis. The POSILAC® Technical Service (TS) Helpline served as a hub for the processing of most of these reports. The Helpline was initiated to answer questions from the dairy industry regarding the use of POSILAC®. Over 7,000 Helpline calls were fielded during the first two years of commercialization. The TS staff also had responsibility for capturing ADE data. Product inquiries arising from Helpline communications, Customer Service Center contacts (telephone orders and general inquiries), the Field Sales Group's record of producer contacts (computerized memopad), and field inquiries were all processed through the St. Louis database.

Inbound and outbound telephone calls at Protiva's Customer Service Center also were used to collect adverse drug experience reports, respectively. Outbound calls were placed as Protiva attempted to follow up with every customer several times after they placed their initial order. The Customer Service Center processed over 240,000 calls during the first two years of sales. During each call, the customer's experience with POSILAC® was queried. Thus, each producer was queried by Customer Service an average of 14 times.

Therefore, a significant difference exists between Protiva's ADE database and the industry norm. Most animal products are marketed through a distributor or by prescription from a veterinarian. POSILAC® is marketed directly to farmers and each customer call is an opportunity to gain knowledge of their farm operation and experience. However, for over a third of the total ADE reports the customer did not know or remember the number of animals treated with POSILAC® or affected with a health disorder. In that case, Protiva and CVM agreed beforehand to estimate the number of cows as follows:

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- 45% of the herd was assumed to be “treated” with POSILAC® based on sales data for in-herd use rates,
- 100% of the treated cows within a herd were assumed to have “not responded” where product efficacy was questioned (milk response is typically measurable only on a herd basis),
- 33% of the treated cows within a herd were assumed to have “reacted” for non-efficacy conditions (45% x 33% = 15% of the total herd), which was a high estimate of the number of cows expected to be affected with mastitis, the most frequently reported health disorder in dairy cows (12 to 13.4%; Hogan et al. 1989; Jones, 1993; Shook, 1985; Bigras-Poulin et al. 1990; NAHMS, 1996), and
- where the customer specified “some” or “few” animals were affected, the number “reacted” was estimated between 2 and 5 depending on the supporting text.

This procedure represented a conservative approach, i.e. over-estimation of animal numbers. For example, unspecified herd incidence of an event such as abortion was thus estimated as 15% (45% x 33%) using this method even though the reported incidence for abortion is no higher than 3.6% (NAHMS, 1996).

FDA Algorithms

Every ADE report is evaluated by a qualified veterinarian at the Center for Veterinary Medicine who codes the data, describes the clinical signs and assigns an algorithm which describes the level of suspicion that the reaction may have been drug-related (Kramer et al. 1979; Oeller, 1995). Causality is assigned based on evaluation of six areas: 1) previous experience, 2) alternate etiology, 3) timing of events, 4) evidence of overdosing, 5) effect of discontinuing and 6) reinitiating treatment.

Data Bases

Protiva’s ADE data was entered into a computer database. Individual reports were submitted also to CVM for entry into their database. Primary differences between the CVM and Protiva databases are listed in Table 1. As a quality assurance check, Protiva’s database includes a routine down-load of CVM’s ADE data for POSILAC®. A computerized process was developed to link that information with Protiva’s ADE data base, the commercial sales database, and an on-line analysis of expected incidence rates. This procedure allowed for timely evaluation of the database and verification of the accuracy of computer entries.

RESULTS

Due to our proactive system for collecting farmers’ experiences with POSILAC®, an improved ADE reporting efficiency could then be anticipated. However, one must be cautious because any animal health condition on a farm where POSILAC® was used could be construed as an ADE. In addition, POSILAC® was the first over-the-counter product of its kind to be marketed directly to the client. Direct marketing enhanced Protiva’s ability to collect a large amount of information on every customer’s experience with POSILAC®.

During the first two years of commercial sales, POSILAC® was purchased by 16,957 clients who manage 3,179,178 cows. During the first two years, 1,439 reports of adverse drug experiences were filed. However, a report of an adverse effect does not necessarily infer the effect was caused by the drug. The CVM deemed that only 64% of the reports (n = 924) were at least possibly related to the use of POSILAC®. The remaining 515 ADE reports were not positively related to POSILAC®.

The pattern of ADE reports by date of onset of the clinical manifestation is shown in Figure 1. The general profile was similar to most new products: increased reporting early in commercialization (Begaud et al. 1994) followed by a gradual decline as customers learn to use the product and gain confidence.

Many of the reports evaluated included multiple clinical signs. For example, a cow with a teat injury also may have mastitis, decreased body weight and an elevated milk somatic cell count, i.e., one report of one cow may have generated four clinical signs. All of the reported clinical manifestations are known to occur in dairy cattle not supplemented with POSILAC®. Based on the label insert for POSILAC®, the following

health categories were specifically evaluated in addition to individual signs: mastitis, increased milk somatic cell counts (SCC), udder abnormality, reproductive disorders, digestive disorders, foot & limb disorders, and injection site reactions. The number of reports of death was also evaluated since, for most veterinary products, death is the most commonly reported adverse drug experience (CVM, 1995).

Based on either the number of herds reporting or the estimated number of cows affected, the reporting of labeled health precautions for POSILAC® was below or within the range of reported incidence (Table 2). This is particularly relevant since the Protiva ADE reporting system intentionally over-estimates the number of animals affected. Reports of all health disorders decreased over time, consistent with the absence of a systematic effect of POSILAC®. The proportion of different health categories was relatively constant across time and consistent with the absence of the following: 1) a cumulative adverse effect of POSILAC®, 2) fad reporting (excessive influence of news media, politics or other external influences) and 3) changes in reporting bias.

The reporting rates for the first two years of commercialization were much lower than some have inferred from the label insert for POSILAC®. For example, clinical mastitis was predicted to be catastrophically increased with the commercial use of POSILAC®. Only 271 reports of clinical mastitis associated with the use of POSILAC® were filed out of 16,957 customers (Table 2). Of those reports, the FDA noted that 33% were not positively related to POSILAC®. The number of mastitic POSILAC®-treated cows noted in ADE reports was at least 30 fold lower than the incidence reported in a survey of the U.S. herd (Table 2). This result was expected; POSILAC® has only a marginal effect on the incidence of mastitis (FOI, 1993).

A second explanation for the low incidence of health disorders reported could be because the data came from ADE reports; reporting rate can be very low for passive reporting systems (Begaud et al. 1994). However, the reporting system for POSILAC® is a combination passive and proactive system. On average each customer had over 14 telephone contacts with the Protiva Customer Service Center. At each call, the customer's experience was queried. A 10x adjustment for unreported incidents (Begaud et al. 1994; Linden, 1993) would still leave the reporting rate or estimated occurrence of health disorders far below the reported incidences in dairy cows. Thus, the label for POSILAC® provides adequate directions for safe and effective use.

The incidence of individual health disorders ranged from 271 reports of mastitis to one report each for 57 other clinical signs. Similarly, less than 1% of the total POSILAC®-treated cows in the U.S. were associated with ADE reports of reproductive disorders (0.4%), digestive disorders (0.7%) or foot/limb disorders (0.3%) compared with the overall reported incidence for U.S. herds, which is 11.6%, 1 to 3.8%, and 2 to 10.5%, respectively (Table 2). Only 92 reports of cow mortality were noted from 16,957 total customers (Table 2). Of those reports, only 32% were categorized by FDA as at least possibly related to POSILAC®. Even using a 10x adjustment for putative unreported incidents (Begaud et al. 1994; Linden, 1993) would still leave the reporting rate or estimated occurrence of health disorders far below the reported incidence of those health disorders (Table 2). Based on the low number of reports and affected cows and the fact that these disorders are commonly reported in dairy cows, the conditions cannot be considered a concern in POSILAC®-treated cows.

CONCLUSIONS

Protiva's unprecedented proactive system for collecting adverse drug experiences during POSILAC® use provides a high degree of confidence that the post-approval monitoring of POSILAC® is effective. The number and severity of the reported health conditions do not indicate new concerns about the safety of POSILAC® for dairy cows. The results of adverse drug experience monitoring strongly support the safety of POSILAC® for use in lactating dairy cows beginning during the 9th week of lactation.

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**TABLE 1
 FUNDAMENTAL DIFFERENCES BETWEEN THE CENTER
 FOR VETERINARY MEDICINE (CVM)
 AND PROTIVA'S ADVERSE DRUG EXPERIENCE (ADE) DATA BASES**

CVM Data Base:	Protiva ADE Data Base:
* Assigns one number of treated, reacted and dead animals for each report (regardless of the clinical signs included in the report).	* Assigns individual numbers of treated, reacted and dead animals for each clinical sign noted within a given report.
* Includes the date the report was submitted to the FDA.	* Includes the date of initial contact for the inquiry, date of onset of clinical sign and date the report was submitted to the FDA.
* Includes a code for country (US vs. ex-US) in which the event occurred.	* Includes nation and state in which the event occurred (for regional trend analysis).
* Does not include estimates of the population from which the ADEs arose.	* Includes the number of doses sold, customers who purchased those dose and the number of cows in their herds (by year, month, region, state).

Figure 1. Total Adverse Drug Experience Reports by sales quarter of onset

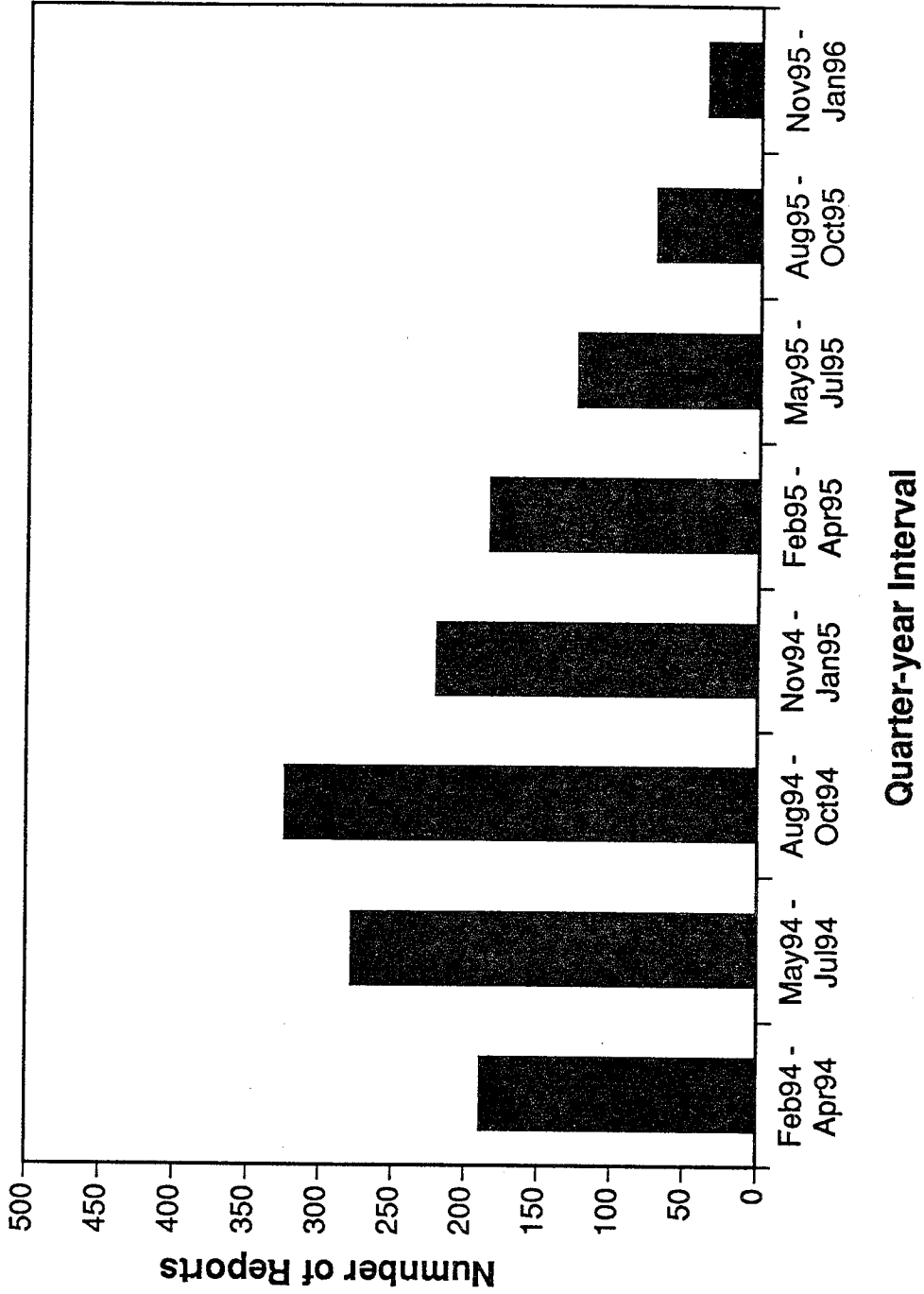


TABLE 2
SUMMARY OF ADVERSE DRUG EXPERIENCE (ADE) REPORTS FOR POSILAC®
IN THE U.S. FROM FEB. 3, 1994, TO FEB. 4, 1996

Health Disorder ¹	Total Number of ADE Reports	U.S. POSILAC®-treated cows ² reported with the disorder (%)	Range of reported incidence in U.S. dairy herd (%)	Reference
Clinical mastitis	271	0.4	12 to 13.4	Hogan et al. 1989; Jones, 1993; Shook, 1985; Bigras-Poulin et al. 1990; NAHMS, 1996
Increased milk SCC	221	0.4	12 to 13.4	Mastitic cows also assumed to have elevated SCC.
Other udder abnormalities	243	0.3	NA ³	
Udder edema during established lactation	113	0.09	0.12	Morrow and Schmidt, 1964; Schmidt, 1971; Lema et al. 1992; Spensley, 1990; Bigras-Poulin et al. 1990
Reproductive disorders ³	283	0.4	11.6	NAHMS, 1996
Abortion	147	0.09	1 to 3.6	NAHMS, 1996; Bigras-Poulin et al. 1990; Klingborn, 1987
Cardiovascular disorders	11	<0.01	NA	
Digestive disorders	249	0.7	1 to 3.8 ³	Guard, 1990; Blood et al. 1979; NAHMS 1996; Fleming, 1990; Bigras-Poulin et al. 1990
Foot/limb disorders	186	0.3	2 to 10.5	Wells et al. 1994; Wells et al. 1993; Dohoo and Martin, 1984; Greenough et al. 1981; Bigras-Poulin et al. 1990; NAHMS, 1996
Hoof disorders	62	0.1	2 to 10.5	Wells et al. 1994; Wells et al. 1993; Dohoo and Martin, 1984; Greenough et al. 1981; Bigras-Poulin et al. 1990; NAHMS, 1996

Lameness	60	0.1	2 to 10.5	Wells et al. 1994; Wells et al. 1993; Dohoo and Martin, 1984; Greenough et al. 1981; Bigras-Poulin et al. 1990; NAHMS, 1996
Injection site reactions	156	0.1	NA ¹	
Mortality	92	<0.01	1 to 3.8	NAHMS, 1996; Milian-Suazo et al. 1988

¹ Many of the reports included multiple clinical signs. SCC = somatic cell count. NA = not available.

² The number of treated cows was calculated as the number of cows owned by POSILAC clients multiplied by the in-herd use rate (45%) = 1,430,630 cows.

³ No estimates were available for "other udder abnormalities" which included the expected secondary signs to mastitis such as udder swelling, hypogalactia and abnormal milk. Reproductive calculations used 60% pregnancy rate. Incidence of displaced abomasum plus incidence of ketosis during treatment period.

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