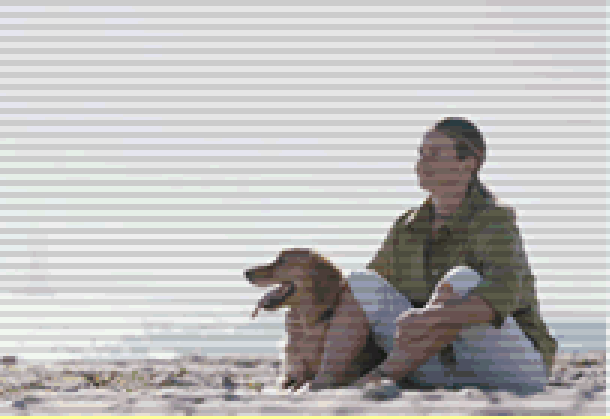
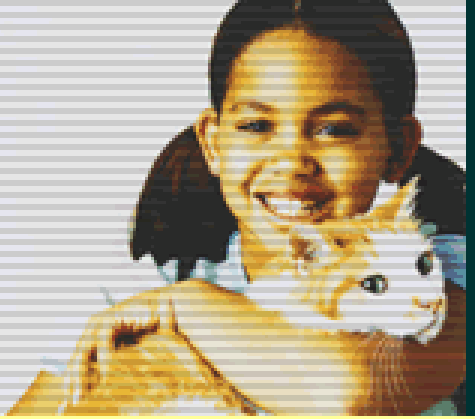




C V M

Adverse Drug Experience (ADE) Reporting System

Food and Drug Administration
Center for Veterinary Medicine

Division of Veterinary Product Safety:

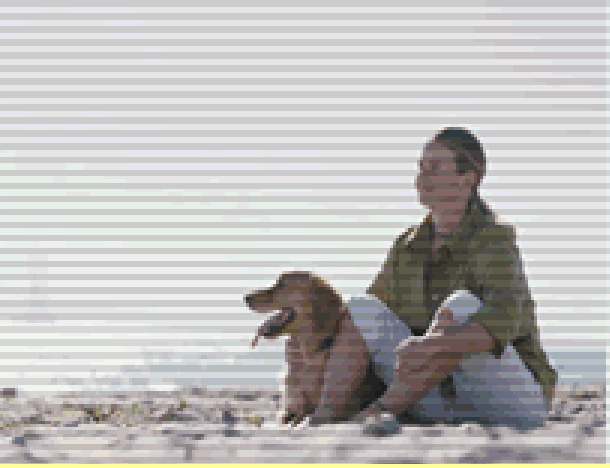
Dr. John Baker, Director

Team Leaders:

Dr. Linda Walter-Grimm, Adverse Drug Event Review Team

Dr. Lee Anne Palmer, Adverse Event Review Team

Dr. Susan Bright, Data Management and Analysis Team



CVM

Pharmacovigilance Staff

Safety Reviewers:

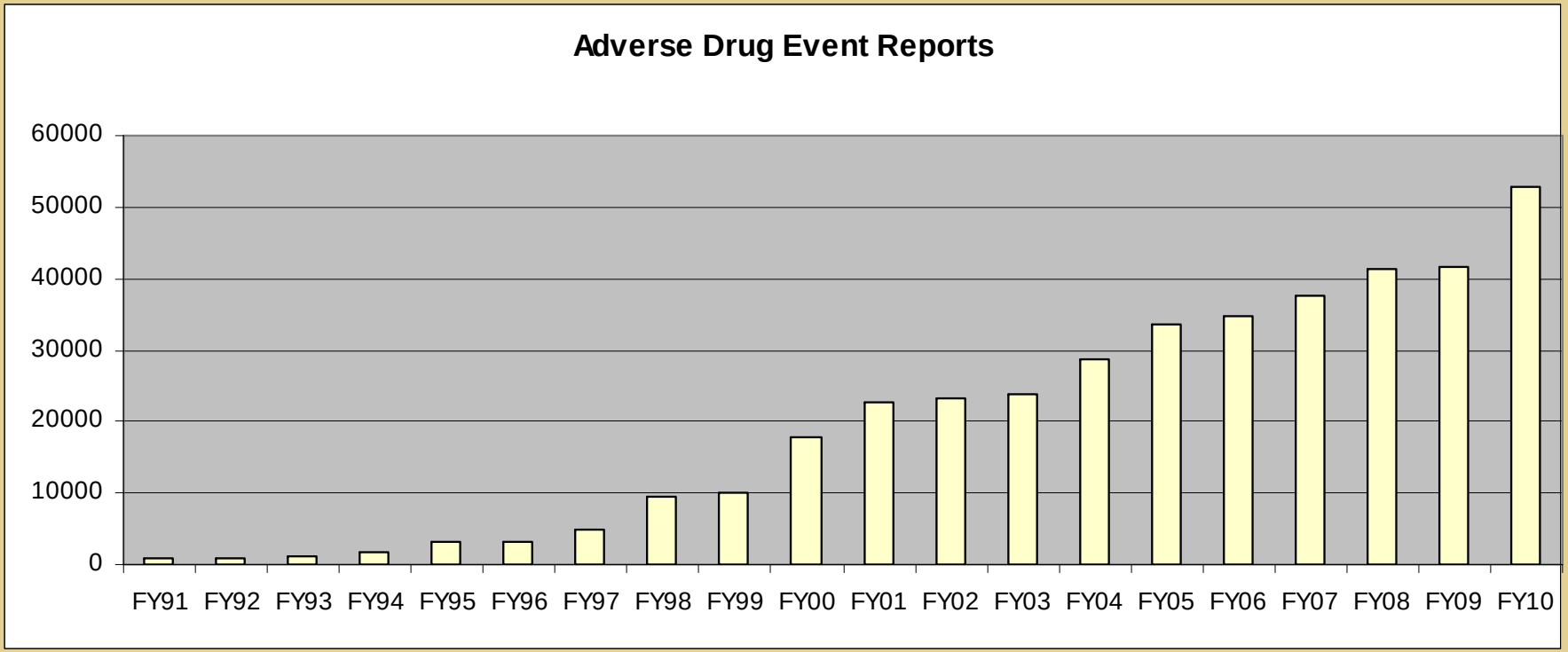
Roderick Hudson, DVM
Teresa Koogler, DVM
Sandi Ehnen, VMD
Tanya Martof, DVM
Amy Neal, DVM
Linda Walter-Grimm, DVM
Tina Burgess, DVM
Priscilla Batten, DVM
Jennifer Smith, DVM
Lee Anne Palmer, VMD (Liaison for pet food adverse events)
Margarita Brown, DVM, MS (Liaison for international adverse events)

Pharmacist: **Linda Kim-Jung, PharmD**
Epidemiologist: **Renee Shibukawa-Kent, VMD, MPH, DACVPM**
Medical Review: **Susan Bright, DVM**

Objectives:

- What is an ADE
- How to report an ADE
- Purpose of the ADE program
- Future of the ADE program

Number of ADE Reports



Adverse Drug Experience (ADE)

An Adverse Drug Experience is any adverse reaction that occurs following the use of a drug product. ADEs can be mild (itching, sneezing) to severe (death). ADEs include complaints of ineffectiveness, product defects and human safety associated with the handling of animal drug products.

Recently Approved Drugs
(less than 3 yrs of marketing)

Reporting of ADEs is especially important for new drugs to complete the safety profile

Since pre-approval data is limited, once newly approved drugs are used in thousands of animals – new safety signals can emerge

Mandatory Adverse Event Reporting for Manufacturers

http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm212682.htm

Electronic Submission Options

Electronic Gateway

- Form 1932
  - Guidance
  - Technical Documents

Safety Reporting Portal

- Rational Questionnaire
  - Guidance

Mandatory Adverse Event Reporting for Manufacturers (Paper Form 1932)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Veterinary Medicine

VETERINARY ADVERSE DRUG REACTION, LACK OF EFFECTIVENESS, PRODUCT DEFECT REPORT

(Forward to address at right. Attach all correspondence that pertains to this reaction.)

Form Approved: OMB No. 0910-0645
Expiration Date: 9/30/2012
(See Burden Statement on page 8.)

Food and Drug Administration
7500 Standish Place (HFV-210), Rm N403
Rockville, MD 20855-9921

NOTE: This report is required by law (21 CFR 514.80 and 512 (l) of the Federal Food, Drug, and Cosmetic Act (FDCA)). Failure to report can result in withdrawal of approval of the application (21 CFR 514.80 (h) and 512 (e) of the FDCA).

The data elements marked with an asterisk [*] require a value or text to be entered. An asterisk at the section level applies to all fields within that section. An asterisk at the subsection level applies to all fields within that subsection. Otherwise, asterisks apply to individual fields.

Part A
Administrative and Identification Information

Regulatory Authority - RA (A.1)*

RA Name	Street Address		
City	State/County or Province	Mail/Zip Code	3-character country code

Marketing Authorization Holder - MAH (A.2)

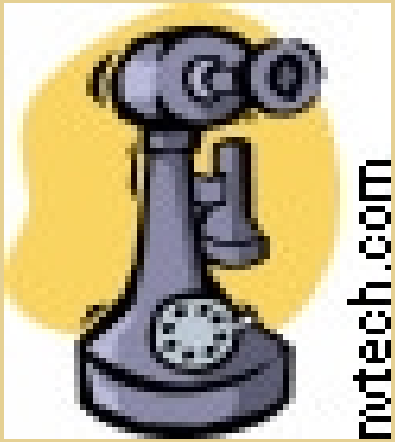
*MAH Information (A.2.1)**

Business Name	Street Address		
City	State/County or Province	Mail/Zip Code	3-character country code

Person Acting on Behalf of the MAH (A.2.2)

Voluntary ADE Reporting - Drugs

- http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm
- By phone :
  - Drug Company's 800 #
  - FDA: 888-FDA-VETS
- By computer
  - download form 1932a



Form 1932A: Mailed From The Consumer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Veterinary Medicine

Form Approved: OMB No. 0910-0645
Expiration Date: 9/30/2012
(See mailer page for Burden Statement)

VETERINARY ADVERSE DRUG REACTION, LACK OF EFFECTIVENESS, OR PRODUCT DEFECT REPORT

(For VOLUNTARY Reporting)

NOTE: This report is authorized by 21 U.S.C 352 (a) and (f). While you are not required to report, your cooperation is needed to assure comprehensive and timely assessment of product labeling.

Individual Case Safety Report Number *(FDA Assigned Number)*	Submission Type ☐ Initial ☐ Follow-up
Report Type ☐ Adverse Event ☐ Product Problem ☐ Both Adverse Event and Product Problem	
Date of this Report *(mm/dd/yyyy)* Month ☐ Day ☐ Year ☐	Date of Initial Report *(If this report is a follow-up) (mm/dd/yyyy)* Month ☐ Day ☐ Year ☐

Sender Information

First Name	Last Name
Street Address	

City	State or Province	Postal/ZIP Code
Country	Telephone Number	Telephone Number (Other)
Fax Number	Email Address	

Sender Category

Reporting a food adverse event

- Website for “How to report a Pet Food complaint”:

http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm182403.htm

- Safety Reporting Portal
  - Pet foods (general public; veterinarians)
  - Reportable Foods Registry:
    - for industry to report problems with foods

https://fpsr2.jbsinternational.com/fpsr/WorkflowLoginIO.aspx?metinstance=3601042E689223E9FDC9643D290EF97D(

Live Search

"CVM CDP SSO enabled appli...

Safety Reporting Portal

Page Tools

HOME ABOUT THE PORTAL SAFETY REPORT DIRECTORY FAQS RELATED LINKS CONTACT US

he Safety Reporting Portal

e Safety Reporting Portal streamlines the process of reporting product afety issues to the Food & Drug Administration (FDA) and the National stitutes of Health (NIH).

hatever your role, (manufacturer, health care professional, researcher, ublic health official, or concerned citizen), when you submit a safety port through this Portal, you make a vital contribution to the safety of merica's food supply, medicines, and other products that touch us all.

Three Ways to Start

- Save a report & finish later
- Faster data entry
- See a list of your reports
- Easier follow up

Not ready to create an account but would like to submit a report?

You can do that here.

EMAIL

PASSWORD

Remember me

Create Account | Report as Guest | Log In | Forgot your password?

Who Should Submit a Safety Report?

Organizations and people in certain professional roles, such as the following, may be required by law to submit safety reports under some circumstances.

- Researchers
- Drug Manufacturers
- Food Manufacturers, Processors, Distributors, and Holders

Others, including concerned citizens, health professionals, and public health officials, may voluntarily submit reports if they encounter safety issues with a product and/or unanticipated harmful effects that they believe are related to a product.

Reports You Can Submit Through this Portal

FDA safety issues involving:

- Human or animal reportable foods
- Animal drugs
- Pet foods

NIH safety issues involving:

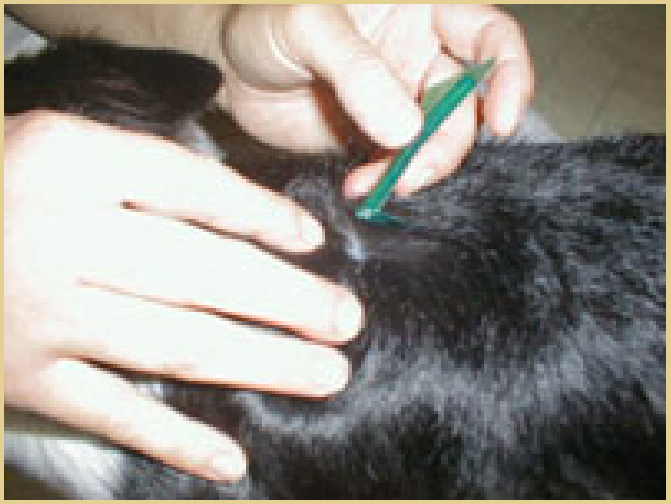
- NIH gene-transfer research

For other issues, find out where to submit your report.

Internet 100%

Reporting a non-drug adverse event

- Veterinary Device: FDA/CVM
  - FDA Form 1932a
- Vaccine Reaction: USDA
  - 800-752-6255
- Pesticide Reaction: EPA
  - 800-858-7378



ADE reports: Current Process

- Reports triaged – manual data entry
- Reviewed: new/recent approvals & hot topics
- Analyze data:
  - evaluate signals/trends
  - develop case series
- MARC meetings
  - interactive cross Center pharmacovigilance forum
  - identify and assess safety signal(s)
  - develop risk mitigation response / plan of action

Case Series

- ADE database provides observational data of a large/diverse population
- A case series is defined which is a summary of descriptive clinical information to characterize the drug's safety profile and risk factors
- A case series commonly includes an analysis of the following:
  - 1. The clinical and laboratory manifestations and course of the event;
  - 2. Demographic characteristics of patients with events (e.g., age, breed, gender);
  - 3. Exposure duration;
  - 4. Time from initiation of product exposure to the adverse event;
  - 5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
  - 6. Use of concomitant medications;
  - 7. Presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071696.pdf

CVM Databases and Programs

- STARS
  - CVM's current Submission Tracking and Review System
- IERS
  - CVM's Information Exchange and Repository Services gateway for receipt of electronic submissions
- PV Works
  - Off the shelf pharmacovigilance software product produced by Assured Information Systems and modified to meet the needs of FDA-CVM

Communication of our information

- Label revisions – PAE sections, warnings, formulation changes, product packaging
- Dear Doctor letters
- Client information sheet
- Freedom of Information (FOIA) requests
- Post-approval risk management programs
- Journal articles
- Cumulative ADE summaries webpage
- CVM Updates (website)

Post-approval ADE section for labels:

- For recently approved drugs, the primary safety reviewer completes an analysis of the ADE database to determine if there are signs to be added to the Post- Approval Experience (PAE) section.
- Periodic review of drug labels may reveal post-approval changes in the safety and effectiveness profile.

FOI (Freedom of Information Act)

Reviewed ADE summaries are available to the public at the FDA website.

http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055369.htm

THIS SITE IS UPDATED MONTHLY

Safety & Health

Product Safety Information

- 3-Nitro (Roxarsone) and Chicken
- Adverse Drug Experience (ADE) Reports
- Animal Drug Shortage Information
- Bovine Somatotropin (BST)
- Dear Doctor Letters
- Letters to Veterinary Professionals
- Steroid Hormone Implants Used for Growth in Food-Producing Animals
- Veterinary Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Resources for You

- Veterinary Adverse Event Voluntary Reporting
- Veterinary Adverse Event Reporting for Manufacturers

Adverse Drug Experience (ADE) Reports

Cumulative Veterinary ADE Reports

1987 to June 30, 2011

- A-C - ADE Summaries (accessible version)
- D-I - ADE Summaries (accessible version)
- J-M - ADE Summaries (accessible version)
- N-S - ADE Summaries (accessible version)
- T-Z - ADE Summaries (accessible version)

In the spirit of openness and transparency, the Center for Veterinary Medicine (CVM) has created and posted these ADE summary reports for the public. These reports include domestic adverse drug experience reports submitted to CVM that we have determined to be at least "possibly" drug related. CVM has posted the Cumulative ADE Summaries Report so that veterinarians and animal owners can have easily available access to information about signs that have been associated with drugs. These reports will be updated on a monthly basis.

ADE Report Description

The primary purpose for maintaining the CVM ADE database is to provide an early warning or signaling system to CVM for adverse effects not detected during pre-market testing of FDA-approved animal drugs and for monitoring the performance of drugs not approved for use in animals. Information from these ADE reports is coded and entered into a computerized FDA/CVM ADE database. CVM scientists use the ADE database to make decisions about product safety which may include changes to the label or other regulatory action.

The Center's adverse drug experience (ADE) process takes into consideration confounding factors such as:

- Dosage

DRUG: AMOXICILLIN

Species: CAT

Route of Administration: ORAL

Sign:	Number of Times Reported:
VOMITING	35
ANOREXIA	19
DEPRESSION/LETHARGY	14
DIARRHEA	13
DEATH	8
INEFFECT, ANTIBIOTIC	7
ALOPECIA	4
FEVER, BODY	4
HYPERSALIVATION	4
RECUMBENCY	4
ANEMIA	3
ATAXIA	3
BEHAVIOR DISORDER	3
CONGESTION, SKIN	3
HYPERACTIVITY	3
PRURITIS	3
WEAKNESS	3
BILIRUBIN(TOT) HI, BLD	2

Future goals

- Outreach
- Sentinel Initiative
- VICH
- Electronic submission
  - Gateway to gateway
  - Safety Reporting portal
- Data mining

Sentinel Initiative

- Develop a national electronic safety monitoring system
  - Strengthen FDA's ability to monitor postmarket performance of medical products
  - Enable FDA to access existing automated healthcare data by partnering with data holders (e.g., insurance companies with large claims databases, owners of electronic health records, others)
  - http://www.regulations.gov/#!docketDetail;D=FDA-2009-N-0192
- Will augment, not replace, existing safety monitoring systems

Potential Capabilities of Sentinel

- Improving FDA's capability to identify and evaluate safety issues in near real time
- Enhancing FDA's ability to evaluate safety issues not easily evaluated with the passive surveillance systems currently in place
  - Expanding FDA's access to subgroups and special populations (e.g., the elderly)
  - Expanding FDA's access to longer term data
  - Expanding FDA's access to adverse events occurring commonly in the general population (e.g., myocardial infarction, fracture) that tend not to get reported to FDA through its passive reporting systems

Evaluation of Potential Data Sources for Animal Drugs Used in Veterinary Medicine

- Contractor: Insight Policy Research, Inc.
- FDA: Office of Critical Path Programs, CVM
- http://www.regulations.gov/#!documentDetail;D=FDA-2009-N-0192-0016
- Project's scope of work is the identification, description, and evaluation of potential data sources and/or data environments
  - (1) utility for post-market surveillance of FDA-regulated drugs;
  - (2) scope, content, structure, quality, and timeliness of data;
  - (3) availability, experience and interest of investigators with knowledge of the data in using it for post-marketing product safety surveillance as well as plans for further data source enhancements;
  - (4) barriers that exist to including each data source in the Sentinel Initiative.

Findings Across Data Partners

- Each section in this chapter assesses the data sources on one of the following four critical study criteria:
- 1) ability to provide high-quality and timely data;
- 2) adequate coverage of the data source;
- 3) suitability or usability of the data source in postmarket surveillance; and
- 4) interest or willingness of the organization (or those that maintain similar data partners) to participate in a national postmarket surveillance system

Project Conclusions and Recommendations

- Challenges and Limitations of Potential Veterinary Medicine Data Partners
- Difficulty in Linking Drug Delivery to Outcomes
- Implications for Postmarket Surveillance of Veterinary Medical Data

Implications for Postmarket Surveillance of Veterinary Medical Data

- 1. Define Data Elements Needed (e.g., Exposures and Outcomes).
- 2. Define Scope of Participation
- 3. Create a Value Proposition
- 4. Engage Industry Leaders and Associations
- 5. Examine Resources FDA Can Offer
- 6. Mitigate Potential Liabilities

VICH *International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products*

- International harmonization of reporting adverse events
  - USA, EU, Japan
    - Canada, Australia
  - standardize definitions
  - standardize data elements
  - standardize dictionaries
  - electronic submission

Electronic Submissions

- Automatic population of the database
- Workflow management
- Identification of emerging problems
- More efficient data mining capabilities, even if the report has not yet been reviewed

CVM ADE eReporting Goals

- Enhanced capabilities for ADE triage
- Increased efficiency of ADE data entry
- Enhanced capabilities for ADE data review
- View the data in the most appropriate way
  - Enhanced data analysis
- Decreased need for paper storage, both on-site and off-site
- Harmonization of data fields will result in firms and CVM relying on “same data”
- Integrate eReporting into CVM’s current tracking system and work processes

What is Data Mining?

- Definition: the use of computer algorithms to analyze data in large, complex databases
- Goal: to discover patterns of associations or unexpected occurrences (i.e. “signals”)
- Impact: once meaningful patterns identified, information can be evaluated for intervention as appropriate
- Specifically, data mining identifies disproportionately high frequencies of occurrence of drug-event pairs relative to “expected”
- “Expected” calculations are limited to database in question

What Data Mining Can Do:

- Signal *potential* problems quickly
- Generate *hypotheses* regarding potential drug safety problems
- Signal events that might be missed if a pattern is not expected

What Data Mining **Cannot** *Do:*

- Data mining cannot *prove* or *refute* causal associations between drugs and events.
  - Data mining simply identifies disproportionality of drug-event reporting patterns
- Data mining cannot *replace* hands-on clinical review
  - Individual review of cases is always necessary to explore data mining signals

Data Mining is a Tool For Finding Patterns…

It Should Not Replace Our Own Eyes or Good Clinical Judgment

Questions?