The Consumer Healthcare Products Association and FDA present

The OTC Drug Seminar Series

Management of Post-Marketing Safety Surveillance Data for OTC Products

Co-sponsorship Agreement

Consumer Healthcare Products Association (CHPA)

and

FDA

Purpose

To promote a better FDA and industry understanding of the unique challenges in the present and future OTC healthcare environment.

Previous Seminars

- Labeling of OTC Drug Products
- OTC Drug Monograph Process
- Advertising of OTC Drug Products
- “OTC Squares”

Steering Committee

Sandy Barnes, FDA
Greg Collier, Procter & Gamble
Leah Christl, FDA
Robert Eshelman, FDA
Sharon Heddish, Wyeth
Michelle Jackson, FDA
Susan James, GlaxoSmithKline
Iris Khalaf, FDA
Lorna Totman, CHPA
Mitch Weitzman, FDA

Today's Seminar

Management of Post-Marketing Safety Surveillance Data for OTC Products

Steven Hermansky

Schering-Plough Corporation

CHPA®

FOUNDED 1881

Consumer Healthcare Products Association

Seminar Overview

- Safety and quality monitoring are important to both industry and FDA
- The principles for managing adverse events for OTC products, NDA or monograph, are consistent
- Post-marketing safety surveillance data represents an important tool in the overall effort to detect and manage emerging safety issues for OTC products.

Product Safety Surveillance is Good Business Practice

Seminar Outline

- Industry presentations
  - Product overview
  - Case collection, reporting and follow up
  - Data review
  - An industry example
- Questions and discussion
- Break

Outline (2)

- FDA presentations
  - Regulatory Aspect of AE Reporting
  - Medical Officer's Approach to Understanding AEs Through Review of Reported Data
  - Post-Marketing Surveillance of AE Reports in ODS
- Questions and discussion

Presenters

- Industry
  - Steve Hermansky – Schering-Plough
  - Leslie Rylander – P&G
  - Sandy Schoenewald – McNeil
- FDA
  - Keith Olin – ONP
  - Steve Osborne – ONP
  - KC Kwon – ODS

Consumer HealthCare Product Spectrum

- Steve Hermansky

Product Spectrum

- General product issues
- Examples of Product types
  - OTC drug products
  - Cosmetics
  - Medical Devices
  - Dietary supplements
  - Pesticides
  - Consumer articles
  - Household products

Product Spectrum

- Consumer HealthCare companies market a wide variety of products
- Many of these products are regulated by FDA
- Some products are not regulated by FDA
- Many other agencies (CPSC, DEA, EPA, DOT, FTC) also regulate our products

Product Spectrum

- Products marketed by Consumer HealthCare companies, regardless of regulations, are monitored for consumer complaints including quality problems and health effects
- Not monitoring these products is poor business practice

OTC Drugs

- NDA
- Monograph

Medical Devices

- Condition treatments
  - Toothbrushes
  - Syringes
  - Denture Fixatives
  - Wart cryotherapy
  - Vaporizers
  - Bandages and cold packs
- Diagnostic kits
  - Pregnancy test kits
  - Blood Glucose test kits

Testing for product quality complaints

- With Denture Adhesive great ingenuity is required

Cosmetics Dietary Supps.

- Shampoos
- Moisturizing creams and lotions
- Skin cleansers
- Sunless tanning agents
- Foot and body powders
- Vitamins and Minerals
- Electrolyte replacements
- Nutritional Products
- Botanicals/Supplements

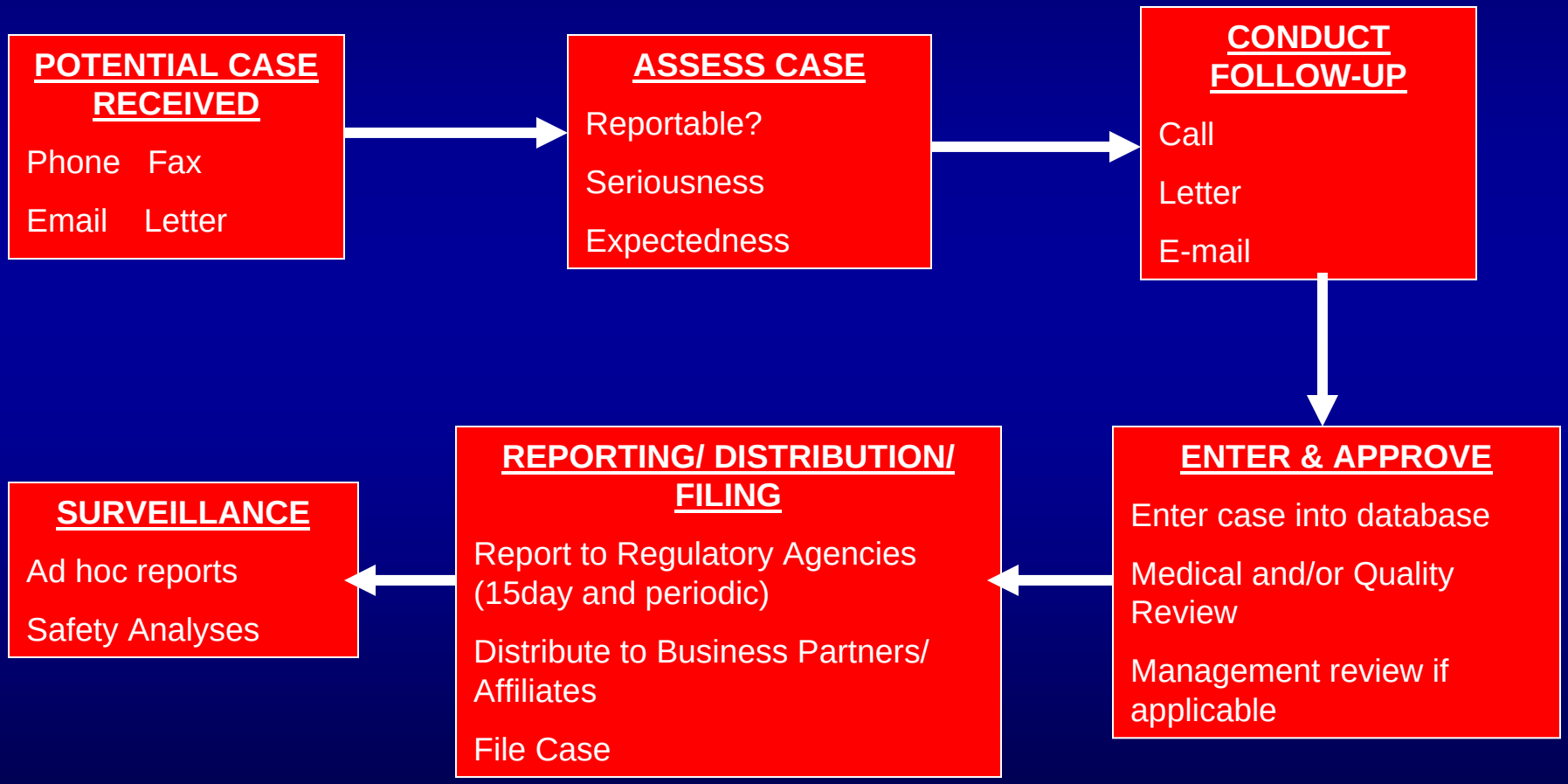
Pesticides Consumer Articles

- Insect repellents
- Headlice treatments
- Scabicides
- Pinworm treatments
- Nail files
- Combs
- Hair trimmers

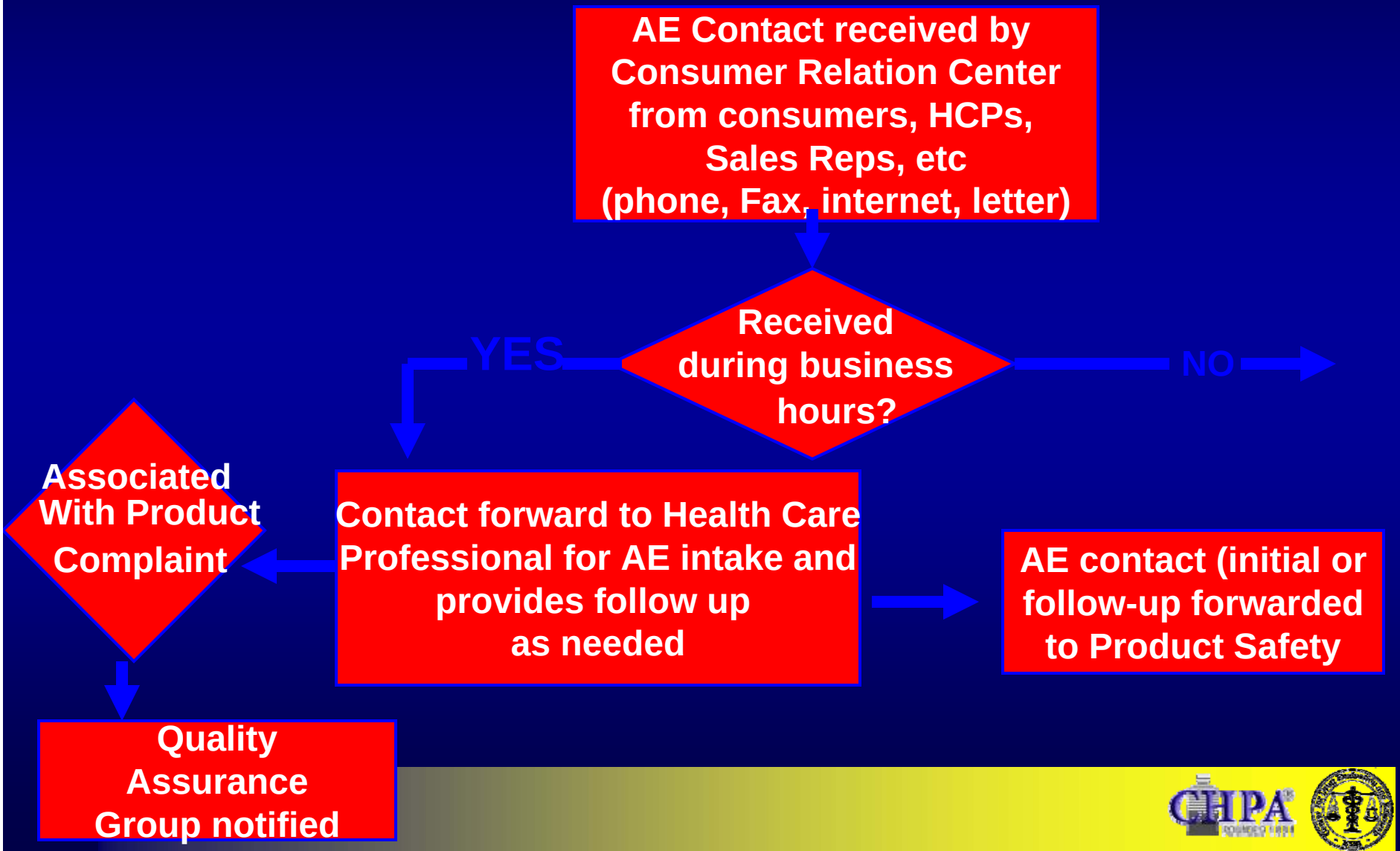
Case Collection, Reporting and Follow Up

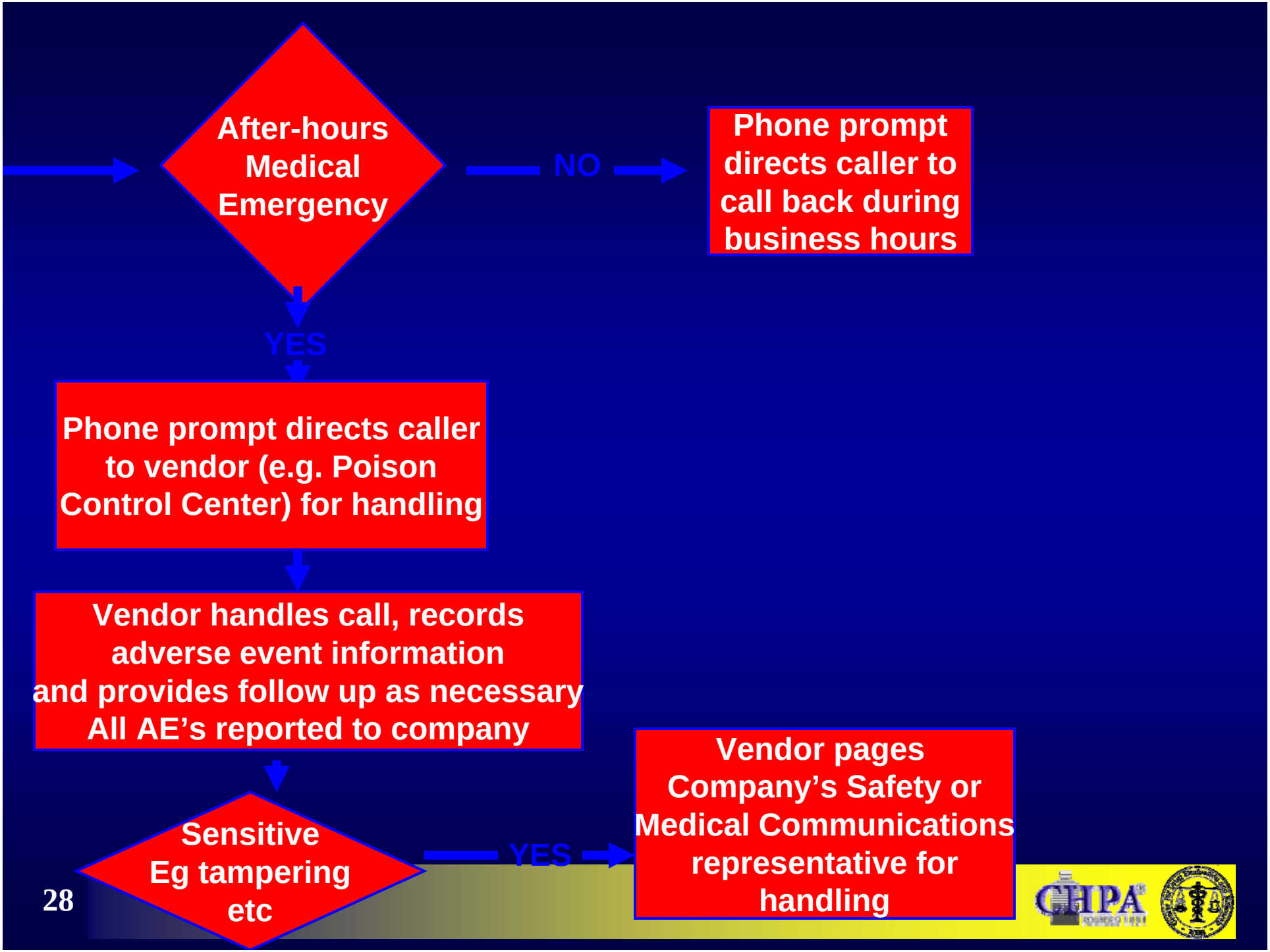
- Sandy Schoenewald

High Level AE Flow

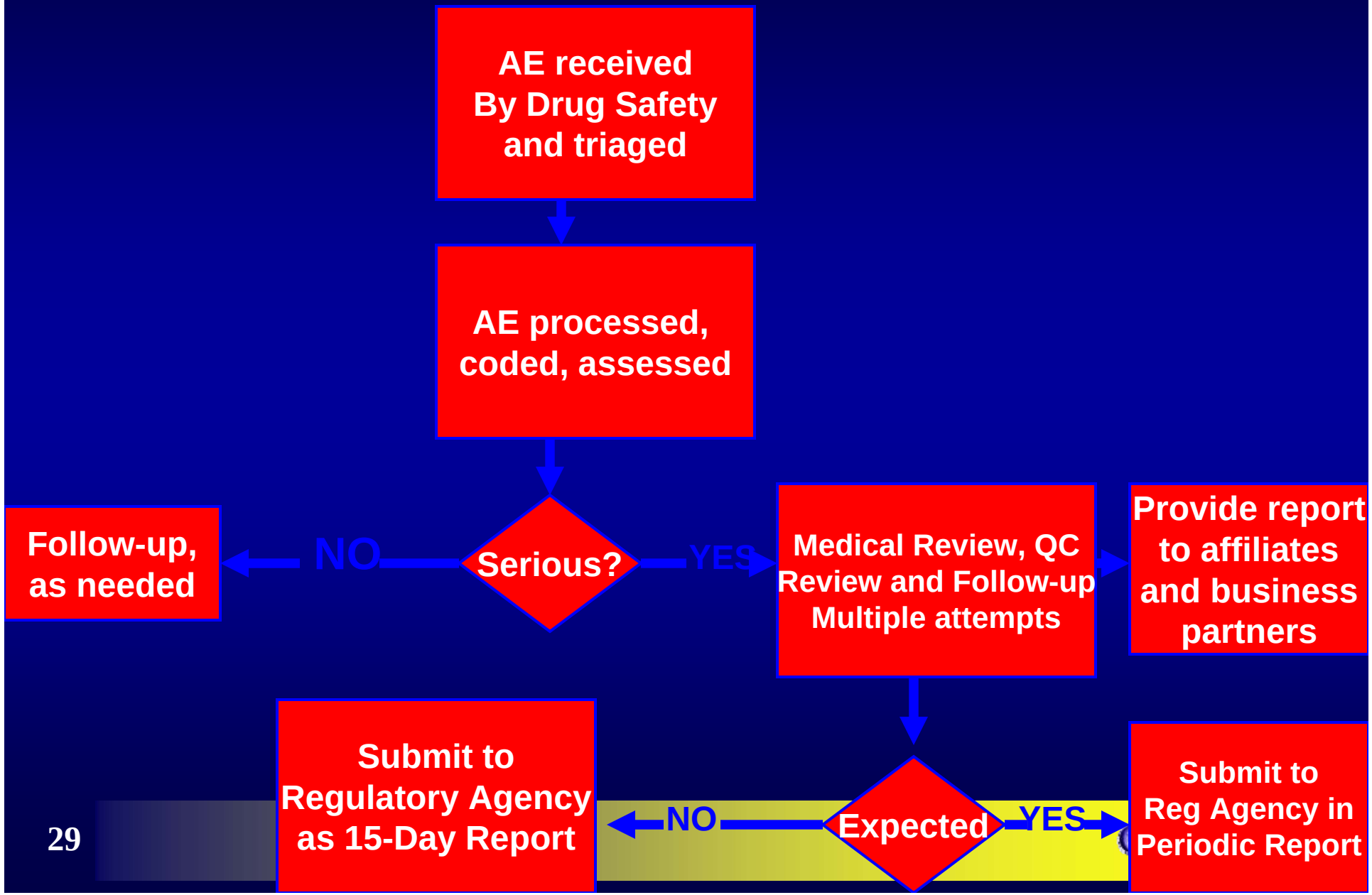


AE Decision Tree




After-hours Medical Emergency
NO
Phone prompt directs caller to call back during business hours
YES
Phone prompt directs caller to vendor (e.g. Poison Control Center) for handling
Vendor handles call, records adverse event information and provides follow up as necessary All AE's reported to company
Sensitive Eg tampering etc
YES
Vendor pages Company's Safety or Medical Communications representative for handling

AE Decision Tree



Follow-up Process

- Dependent upon case type
  - Serious, potentially serious or cases of interest:
    - May include phone call and multiple postal letters
    - Also, questionnaire and/or medical records authorization
- Barriers
  - Consumers may
    - not provide phone number or mailing address or may not provide accurate contact information
    - refuse additional or follow-up contact with manufacturer
    - refuse to complete authorization for medical records
  - Health care providers may refuse to provide information because of misunderstandings about HIPAA

Data Review

- Leslie Rylander

Data Review

- Ongoing review for Safety Signals based upon individual case review
- Periodic review for trends or changes in data

Data Review

- Ongoing (individual case review)
  - All serious AEs are reviewed as data are received
    - Causality
      - Pharmacologically relevant?
      - Interactions
        - » Drug/drug
        - » Drug/disease
      - Other contributing factors?
    - Other, similar reports received?
      - Recently
      - Historically
  - Does this case represent a significant Safety Signal?

Data Review

- Periodic (formal review of recent history)
  - Frequency/rate as compared to history
  - Frequency/rate changes between lots of products
  - **Advantage of OTC is availability of Lot Number**

Data Review

- Follow up
  - Possible Safety Signal identified
    - Initiate medical investigation
    - Initiate quality investigation
    - Management communication required
  - Must come to resolution per procedures
    - Action plan prepared
    - Notification of FDA as appropriate

An Avalanche of Information but only a Small Amount of Data

- Steve Hermansky

Consumer Contacts at 1 Company 2003

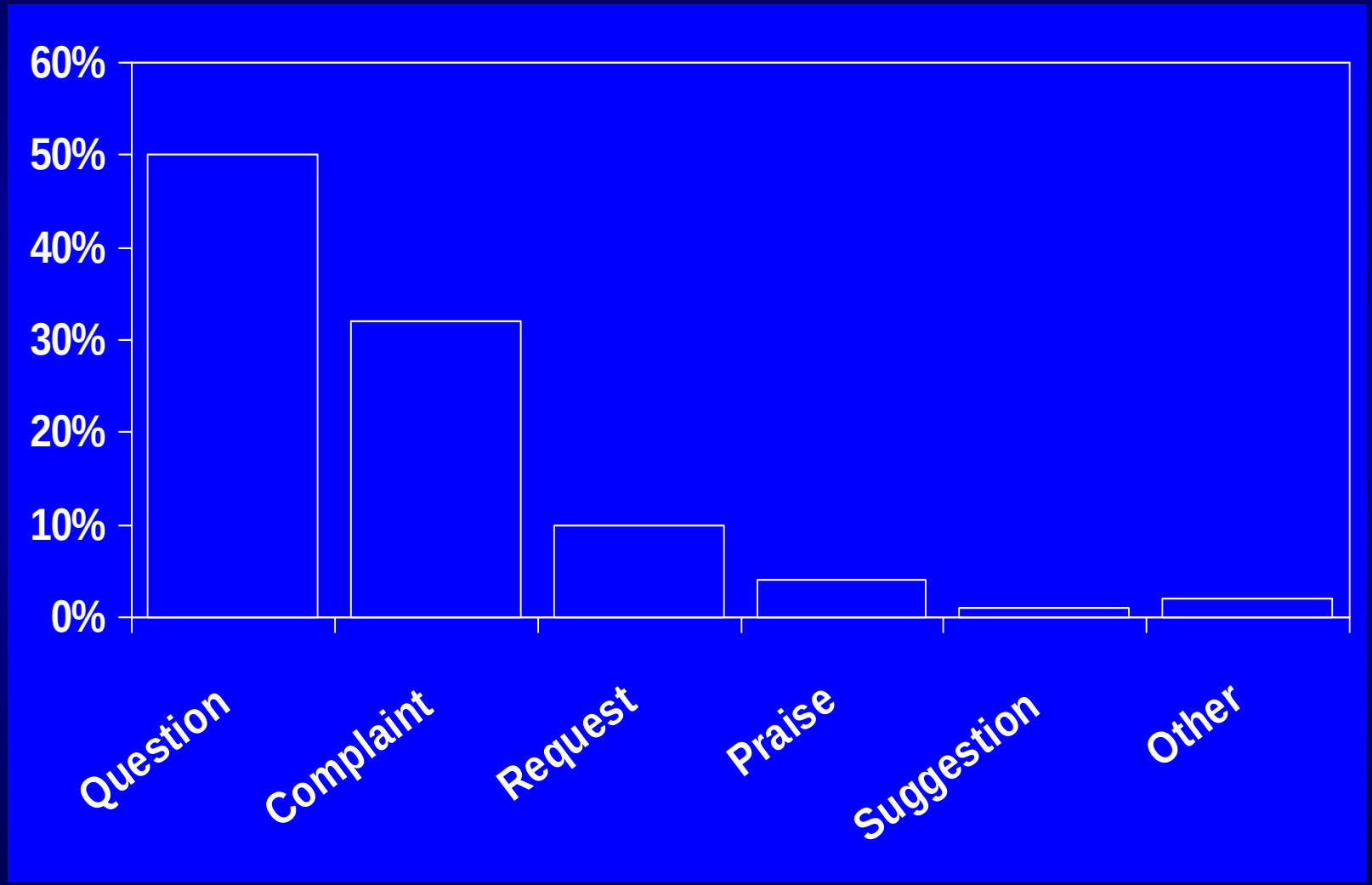
Contact Method	# Cases	% Total Cases
Phone	**136,459**	**81%**
Internet	**23,845**	**14%**
Mail	**7,833**	**5%**
Fax/Convention/Other	**82**	**<1%**
TOTAL	**169,219**	**100%**

230,000 Issues

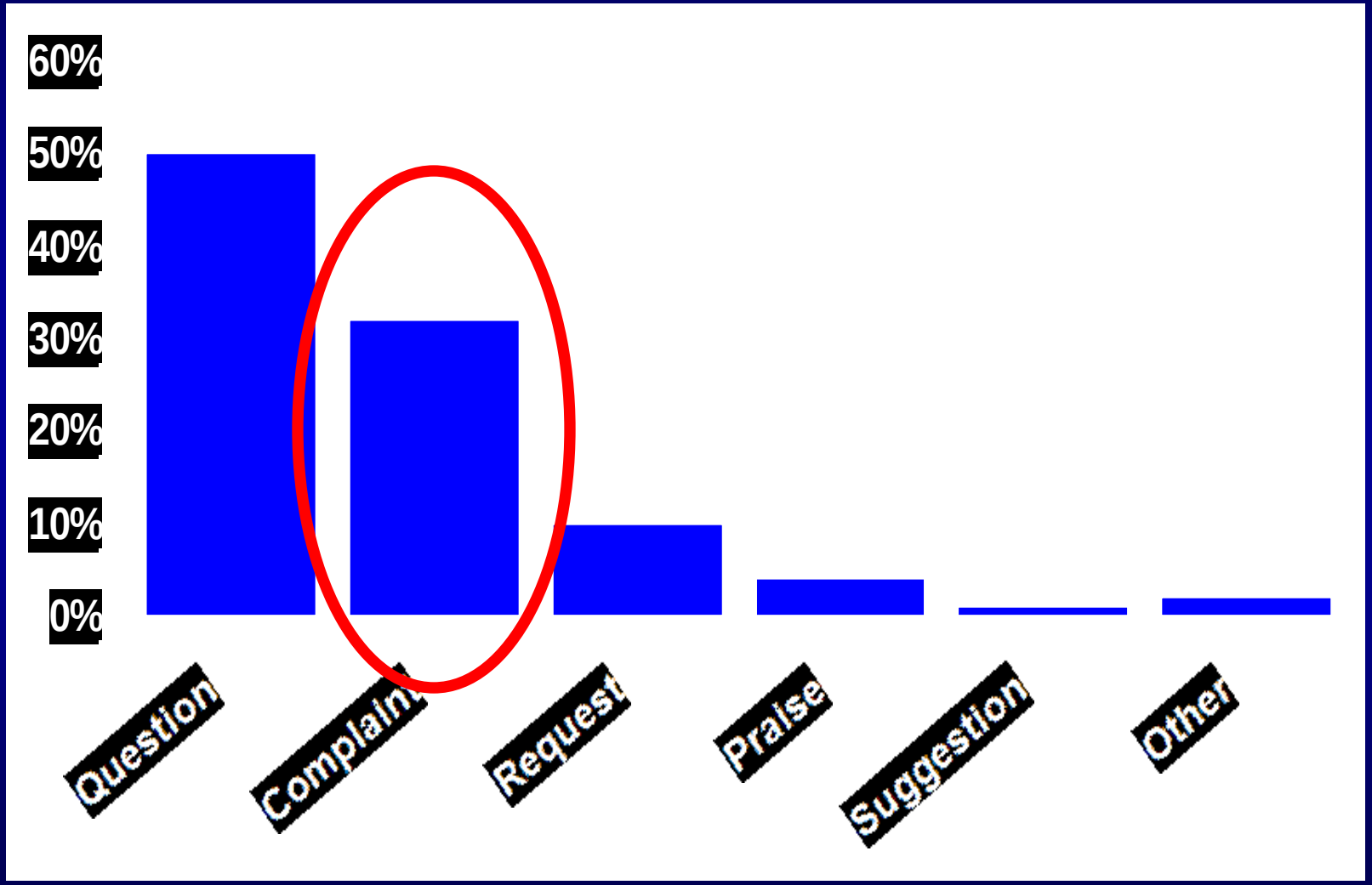
Numbers of Products Covered by 800# in 2003

Product Type	Number of Products
NDA	**6**
Monograph	**63**
Dietary supp	**13**
Device	**11**

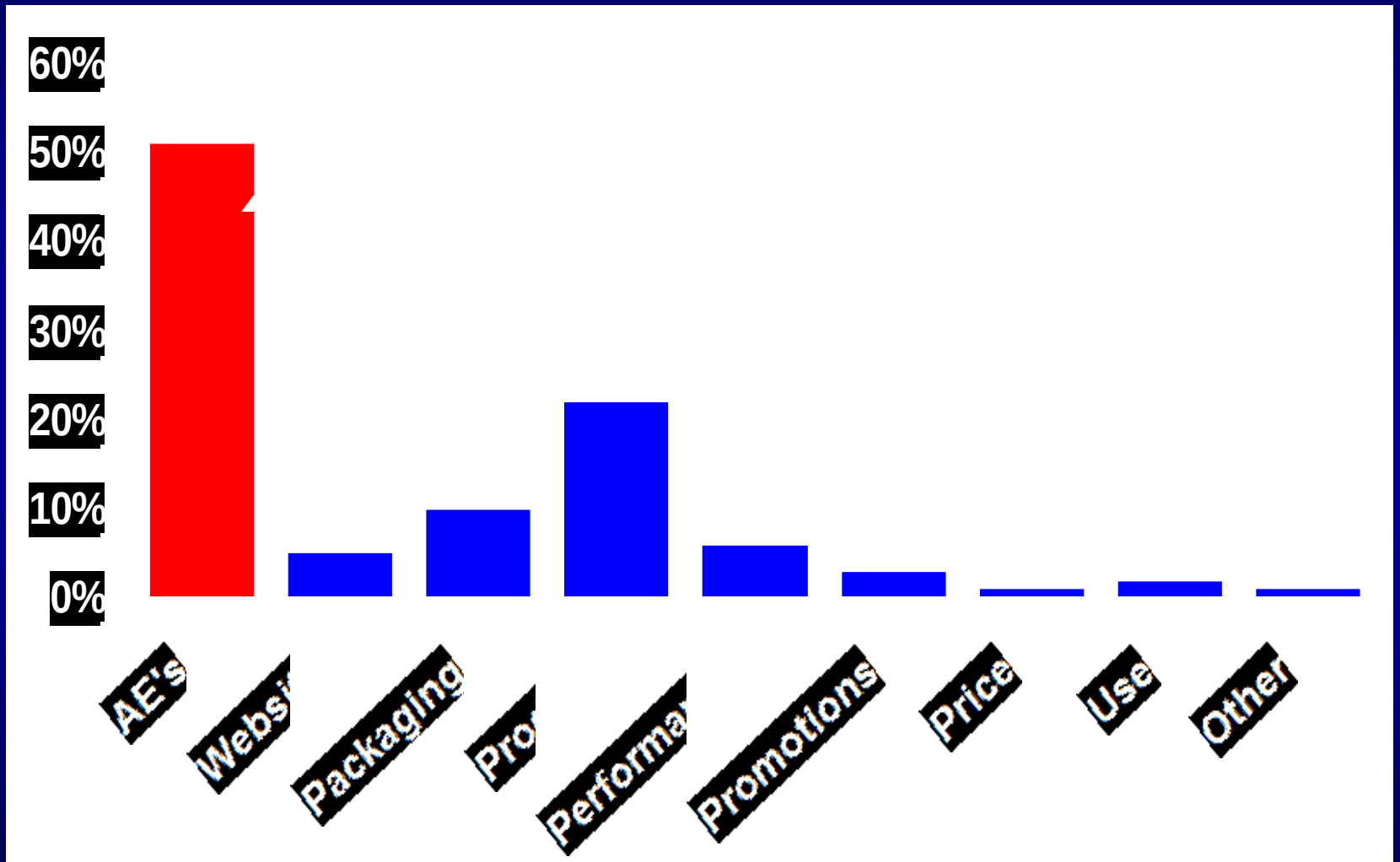
Contacts by Classification



Contacts by Classification



Complaints by classification



Contact/Month By Medium

	#	Phone	SAE's	HCP Calls	SAE's	EMail	SAE's	Cons Letter	SAE's
NDA	**6**	**3517**	**15**	**181**	**0**	**931**	**1**	**359**	**0**
Monog	**63**	**6367**	**7**	**36**	**0**	**1161**	**1**	**209**	**10**
Diets	**13**	**1561**	**2**	**8**	**0**	**386**	**1**	**39**	**0**
Device	**11**	**2376**	**1**	**2**	**0**	**90**	**0**	**280**	**0**

1 Year Pre and Post switch AE's

	Total AE's	SAE's	SAE's/ Standard Unit
Product 1 pre	793	33	0.11
Product 1 post	7228	21	0.042
Product 2 pre	366	39	0.0043
Product 2 post	5021	54	0.0096
Product 3 pre	175	9	0.005
Product 3 post	3643	29	0.01

Conclusion

- Huge number of consumer contacts
- Highly diverse issues called about
- Very few SAE's in light of number of contacts
- Industry takes this very seriously
- Handled the same way as in Rx company

Thank You

Adverse Events Reporting Requirements

•LCDR Keith Olin

•Regulatory Project Manager FDA

What is an Adverse Event?

- Sec. 314.80 Postmarketing reporting of adverse drug experiences
- (a) *Definitions.* *Adverse drug experience.* Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following:
  - An adverse event occurring in the **course of the use of a drug product** in professional practice
  - an adverse event occurring from **drug overdose** whether accidental or intentional
  - an adverse event occurring from [**drug abuse**; **drug withdrawal**;] and any **failure of expected pharmacological action.**

Over-the-Counter Drug Products

- NDA
  - Over-the-Counter (OTC) Products & Prescription Products (Rx)
    - Example: Advil (OTC)
- ANDA
  - Generic Drug Products – Rx & OTC
    - Example: ibuprofen
- Monograph Drug Products
  - OTC
    - Example: acetaminophen

FDA Regulations

- NDA
  - 21 CFR 314.80
- ANDA
  - 21 CFR 314.98
- Monograph Drug Products
  - 21 CFR 330.1

Adverse Events Reporting

- Monograph Drug Products
  - Do not have requirements under the monograph system to report adverse events to the FDA
  - Published Literature
  - MEDWATCH (voluntary)
    - AERS data$_M$ ART
  - Many firms collect and evaluate adverse event information
  - Identify product quality issues
  - Identify product safety risks

products marketed under NDAs?

- Periodic reports
- Annual reports
- Medwatch (voluntary)
  - AERS Data MART
- Published Literature

NDA Requirements

- 21 CFR 314.80 – Post marketing reporting of adverse drug experiences
  - Definitions of different types of adverse events
  - Type of adverse event reports
- Periodic Reports (21 CFR 314.80, 314.98)
- Annual reports (21 CFR 314.81)

Purpose of Postmarketing AE Reporting Requirements

- Identify any safety concerns that have not been previously recognized in a particular drug
  - Examples:
    - Identify previously unknown drug/drug interactions
    - Identify susceptible subpopulations
      - concurrent medical conditions
      - Age/gender issues

FDA Roles

Role of the FDA reviewer

- Understanding and analyzing adverse event data
- The manner in which the MO receives adverse event data, then categorizes the data and assesses causality, and then makes a recommendation, if needed

Role of Office of Drug Safety

- Postmarketing surveillance database and programs
- Safety monitoring activities

CHPA-FDA Post-Marketing Safety Surveillance Seminar

- The Medical Officer's Approach to Understanding Adverse Events Through Review of Reported Data

Disclaimer

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- The opinions expressed are those of the speaker, and do not necessarily represent those of the Food and Drug Administration.
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Adverse Event (AE)

- **Definition**:
- unwanted effects that occur and are detected in a population
- term used whether there is or is not any attribution to a drug
- also known as adverse reaction, or adverse drug reaction
-

Adverse Events (AEs)

- **Types of AEs**
  - Death
  - serious unlabeled
  - serious labeled
  - non-serious unlabeled
  - non-serious labeled

Adverse Events (AEs)

- **Serious AE:** results in death, is life-threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization or prolongation of existing hospitalization, or is a congenital anomaly/birth defect.
- In addition, a medical event that might jeopardize the patient or require intervention to prevent a serious outcome (above).

- **Non-serious AE:** not a serious AE; however—
- nature, severity, specificity, or outcome are not consistent with the information included in the Core Data Sheet.

Serious Adverse Events

- **Always a serious AE**
- Death
- Life-threatening AE
- Persistent or significant disability/incapacity
- Required in-patient hospitalization, or prolonged hospitalization
- Congenital anomaly or birth defect
- Events that jeopardize the patient or require intervention to prevent any of the above

Serious Adverse Events

- **Examples**
- Requiring hospitalization:
- – anaphylaxis
- Not requiring hospitalization, but could jeopardize:
- – allergic bronchospasm - brief emergency
- room treatment
- – seizure
- – blood dyscrasia

Non-serious Adverse Events

•Not a serious AE unless accompanied by a serious outcome

- Overdose
- Pregnancy
- Pre-planned hospitalization

Adverse Reaction

- An undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence
- i.e. drowsiness from a “sedating” antihistamine

Drug Safety Concepts

- pharmacovigilance
- clinical trial AE reporting
- postmarketing AE reporting
- risk-minimization plan
- label warning
- product withdrawal

Adverse Events (AEs)

- **Organ Systems**
  - body as a whole (BW)
  - digestive system (DS)
  - respiratory system (RS)
  - nervous system (NS)
  - musculoskeletal system (MS)
  - skin and appendages (Skin)
  -
  -

Adverse Events (AEs)

- **Organ Systems**
- urogenital system (UG)
- special senses (SS)
- cardiovascular system (CV)
- metabolic and nutritional disorders (MN)
- hemic and lymphatic system (Heme)
- psychiatric (Psy)
-
-

Symptoms

Organ	Less-Worrisome	Worrisome
BW	malaise	fever
DS	nausea	jaundice
RS	rhinitis	dyspnea
NS	somnolence	seizure
MS	leg cramps	tetany
Skin	dry skin	Stevens-Johnson

Symptoms

Organ	Less-Worrisome	Worrisome
UG	urinary frequency	hematuria
SS	dry eyes	deafness
CV	none?	syncope
M&N	weight gain	hypoglycemia
Heme	bruising	thrombocytopenia
Psy	abnormal dreams	mania

Other Worrisome AEs

- anaphylaxis
- aplastic anemia
- arrhythmia
- blindness
- cerebral hemorrhage
- chest pain
- convulsion
- deafness
- hepatotoxicity
- palpitations
- QT prolongation
- pharyngeal edema
- psychosis
- rhabdomyolysis
- seizure
- suicide

Product-Specific AEs

- **Types of AEs**
  - labeled
  - unlabeled
  - common (often>1%)
  - less common
  - drug-related
  - non drug-related

- Medical officer has data from clinical trials, but may or may not have data from marketplace.

Product-Specific AEs

- **Clinical trial data:**
  - total number exposed
  - treatment duration
  - patient-days exposure
  - extent of exposure
  -

Capturing AEs

- **Terminology**
- Terms can differ between reports:
- hepatocellular damage vs. ALT increased
- hypertension vs. BP increased
- troponin increased vs. myocardial infarct
- brain herniation vs. hernia
- anaphylaxis vs. laryngeal edema
- Alternative terms can affect safety signal

AE Terminology MedDRA

- **MedDRA Coding: November 1997**
- 10 times (or more) the size of COSTART
- permits multilevel grouping of terms
- hierarchical structure allows specific terms

- System Organ Class (26)
- – highest level, broadest concept
- High Level Group Term (334)
- – used to group high level terms to aid data retrieval
- High Level Term (1663)
- – links related individual terms

Triggers for Follow-up

- Unlabeled serious symptom
- Clustering of reports with same serious symptom
  - related to medication
  - related to reporting
- Clustering of reports with same non-serious symptom

Is AE related to the drug?

-
- related
- possibly related
- unlikely related
- not related

- Assessment could differ between reporter, sponsor, medical reviewer

Medical Officer Wish List

- AE Reports should contain:

1. consistent coding
- 2. complete data (gender, age)
- 3. structure reports to fit review template
-

Blank

-
-
-
-
-
-

Question #1

- What is the most common adverse event for topical antifungal drug products for the athlete's foot indication?

- a. rash
- b. common cold
- c. impotence
- d. no response to treatment

Question #2

- What is the most common adverse event for topical nicotine replacement products for the smoking cessation indication?

- a. rash
- b. nightmares
- c. hallucination
- d. no response to treatment

Question #3

- What would a medical officer like to see in AE reporting?

1. scattered data
- 2. zero adverse events
- 3. consistent reporting
- 4. report designed to fit review template

Question #4

- What is a likely “labeled” adverse event of a non-antihistamine-containing OTC cough-cold medication?

a. hair loss
b. nervousness
c. leg cramps
d. drowsiness

Question #5

- Which of the following are serious adverse events associated with use of an OTC analgesic?

a.pregnancy
b.stomach ache
c.aseptic meningitis
d.drowsiness

Post-marketing Surveillance of Adverse Event Reports in the Office of Drug Safety

- Hyon (KC) Kwon, PharmD, MPH
- Safety Evaluator
- Division of Drug Risk Evaluation
- Office of Drug Safety, CDER, FDA

- FDA-CHPA Seminar
- November 16, 2005

Outline

- The Office of Drug Safety overview
- Post-marketing surveillance database
- Review and evaluation of adverse event reports

Office of Drug Safety (ODS) Background

- ~100 staff members
- Multidisciplinary (nurses, pharmacists, physicians, scientists, etc.)
- Roles: Safety Evaluators, Epidemiologists, Medical Officers, Health Science Analysts, Project Managers, Contract Specialists, Information Technologists, Administrative Support Staff

Office of Drug Safety (ODS)

- Mission: To evaluate drug risks and promote the safe use of drugs by the American people

- Three Divisions Within ODS:
  1) Division of Drug Risk Evaluation (DDRE)
  2) Division of Surveillance, Research and Communication Support (DSRCS)
  3) Division of Medication Errors and Technical Support (DMETS)

Importance of Drug Safety Surveillance

- Limitations of clinical trials
  - Size of patient population studied
  - Narrow population, often not providing for special groups (elderly, children, women, ethnicity, pregnancy)
  - Narrow indication
  - Short duration

Serious Adverse Event (Regulatory Definition)

Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life Threatening
- Hospitalization
- Disability
- Congenital Anomaly or Birth Defect
- Important Medical Events Based on Clinical Judgment
  - **may jeopardize the patient or subject and**
  - **may require medical or surgical intervention to prevent one of the other outcomes**

FDA's Adverse Event Reporting System (AERS) Database

- Voluntary, "spontaneous" reporting system
- Computerized database
- Origin 1969
- >3 million reports in database
- Contains adverse event reports for drugs and therapeutic biologics
- Exception = vaccines
  VAERS 1-800-822-7967

Types of Adverse Event Reports

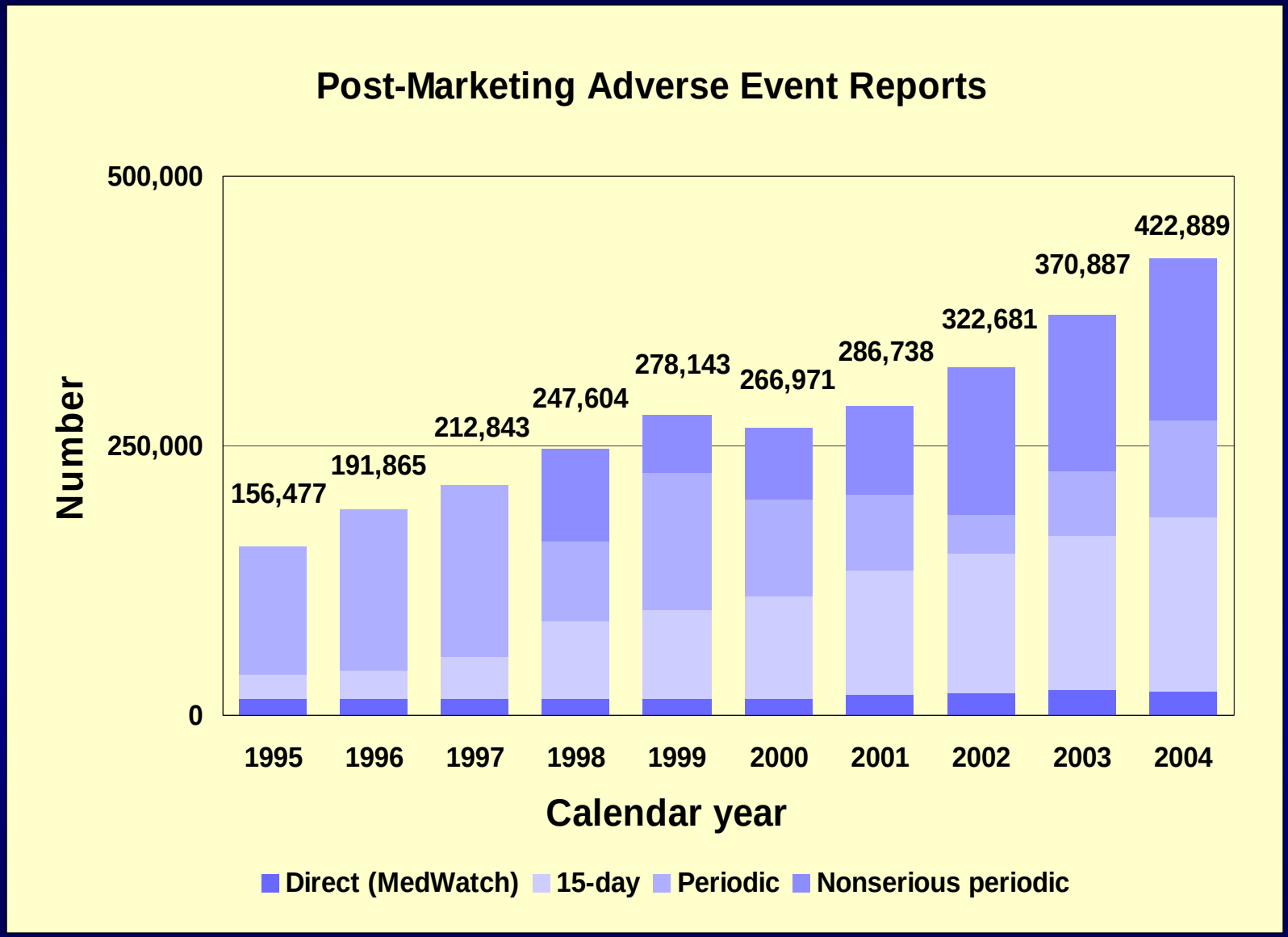
- Manufacturer Reports (mandatory): ~94% of reports
  - From manufacturer (i.e., literature, health care professional and consumer reports) to FDA
  - 15-day reports
    - Foreign and domestic, serious and unexpected (unlabeled)
  - Periodic reports
    - Quarterly for 3 years from approval, then annually
    - Narrative summaries and analysis during period
- Direct Reports: ~6% of reports
  - From health care professionals and consumers direct to FDA

The FDA Safety Information & Adverse Event Reporting Program

- Voluntary reporting by healthcare providers and consumers
- Receives reports for drugs, dietary supplements, biologics, and devices directly to the FDA
- Encourages reports of serious adverse events, product problems, and medication errors:
  - Telephone: 1-800-FDA-1088
  - Online: www.fda.gov/medwatch
  - Fax: 1-800-FDA-0178
  - Mail: postage-paid form on website

MedWatch

- New MedWatch voluntary reporting forms 3500 (voluntary) and 3500A (mandatory) available November 1, 2005
- MedWatch participates in disseminating new safety information to the public:
  - Safety Alerts posted on website (Dear Healthcare Provider letters, class 1 recalls, public health advisories, & safety-related labeling changes)
  - Safety Alerts disseminated via e-mail notification to MedWatch listserve


Post-Marketing Adverse Event Reports
500,000
250,000
0
Number
156,477
191,865
212,843
247,604
278,143
266,971
286,738
322,681
370,887
422,889
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
Calendar year
Direct (MedWatch)
15-day
Periodic
Nonserious periodic

AERS Strengths

- Includes all U.S. marketed products
- Simple, inexpensive reporting system
- Detection of events not seen in clinical trials
- Especially good for events with rare background rate, short latency
- Case series evaluation: identification of trends, possible risk factors, clinical significance of emerging safety concerns

AERS Limitations

- Underreporting
- Duplicate reporting
- Variable reporting quality
- Reporting biases
- Unknown numerator (# of events in population) & denominator (# of exposed patients)
- Spontaneous report numbers cannot be used to determine incidence of adverse events
- Difficult to attribute events with high background rate, long latency

Factors Affecting Reporting of Adverse Events

- Nature of the adverse event
- Type of drug product and indication
- Length of time on the market
- Regulatory action
- Media attention
- Extent and quality of manufacturer's surveillance systems
- Reporter factors: time constraints, uncertainty of drug relationship to event, fear of litigation, desire to publish

Safety Evaluator

- Main mission – To identify and monitor "safety signals"
  - Previously unrecognized (unlabeled) adverse events
  - New drug interactions
  - Increased severity of a known (labeled) event
  - Newly identified at-risk population
- Review of reports –
  - AERS "in-box" reports: all serious & unlabeled, direct serious, some periodic, 'enhanced pharmacovigilance' reports
  - Periodic safety reports
  - Literature
- Work with ODS epidemiologists, OND medical officers

Investigation of Potential Safety Signals

- A safety question is raised – in-box report, periodic safety report, study results, medical literature, outside inquiry, etc
- Develop a case series
  - Use AERS and published literature
  - Thorough database search strategies based on coding terminology using MedDRA
  - Use defined case criteria and case definitions

Assessing Causality*

- For any individual case report, it is rarely possible to know whether the event was caused by a drug product
- Appropriate temporal relationship
- Relationship between disease, drug exposure, adverse event
- Concomitant drug usage
- Medical, laboratory findings
- Dechallenge, rechallenge
- Plausibility

*http://www.fda.gov/cder/guidance/6359OCC.htm

Assessing Causality (2)

- Known drug class effects
- Support from pre-clinical studies, clinical trials
- Absence of alternative explanations
- Look for trends & patterns of events
- Identify risk factors
- Evaluate strength of evidence for causal relationship
- Assess clinical significance

Adverse Event Report Evaluation: Challenges

- Attribution to drug exposure difficult for events with
  - High background rate
  - Long latency
- Often confounded by other possible etiologies
- Absence of complete diagnostic information

Epidemiologic Analysis

- Reporting Rates

  = cases/estimated usage (e.g., dispensed prescriptions)
  - Compare with background rates
  - Compare to drugs within the same class
  - Compare to drugs for similar indication
  - Difficult to interpret
- May pursue further study in longitudinal databases - Cooperative Agreements
- Review and analysis of Phase IV studies

Communication of Safety Information within FDA

- Maintain open communication and collaborative efforts with OND
- Pre-approval Safety Conferences
- Regular Safety Conferences with OND
- Respond to safety questions – formal consult, email, in person
- Written communication – summary and analysis of specific safety issue or overall safety issue of a product
- Assist in decision-making process for safety-related regulatory action

Potential Regulatory Actions

- Labeling change
- "Dear Doctor" / "Dear Health Care Professional" letter
- Risk management plan/program*
  - Targeted Education and Outreach
  - Reminder Systems
  - Fail-Safe Systems

  *http://www.fda.gov/cder/guidance/6358fnl.htm
- Suspension of marketing

Websites to Find Out More

- Office of Drug Safety
  http://www.fda.gov/cder/Offices/ODS/default.htm

- Adverse Event Reporting System

  http://www.fda.gov/cder/aers/default.htm

  - Reporting Regs, Guidances, and updates

Implementation Team

- **Kenric Barclay**
- Tia Frazier
- Steve Hermansky – co-chair
- **Iris Khalaf**
- Hyon (KC) Kwon
- Keith Olin
- Steve Osborne – co-chair
- Leslie Rylander
- Sondra Schoenewald

Special Thank You

- Leah Christl (Steering Team Co-chair)

New Steering Committee

FDA

- Sandy Barnes
- Mike Koenig*
- Bob Eshelman
- Michelle Jackson
- Iris Khalaf

CHPA/Industry

- Greg Collier*
- Sharon Heddish
- Sue James
- Lorna Totman

* Co-chair

Slides

Public Website

http://www.fda.gov/cder/Offices/OTC/industry.htm