Introduction to Pharmacovigilance

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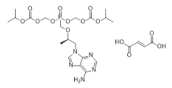
Objectives

- Explain advancements in Health Technologies focusing on the expected and actual outcomes
- Define and understand the goal of pharmacovigilance
- Recognize the role of Pharmacovigilance in the drug development process
- Understand the process by which adverse events are collected
- Become familiar with spontaneous and clinical trial adverse event reports
- Understand Regulatory reporting requirements


Health Technologies:
Expected and Actual Outcomes

Great Expectations from Health Technologies

"…Yet while many know first hand of the relief and healing that drugs can bring, few realize the extent of their potential dangers. In some cases, the Cure can be far worse than the disease."

Drugs That Heal Sometimes Harm
JANE E. BRODY

September 7, 1977, Page 61 | The New York Times Archives

https://www.nytimes.com/1977/09/07/archives/drugs-that-heal-sometimes-harm-personal-health.html

Health Technologies & unintended outcomes: Adverse Reactions

Medicine	Adverse reaction
Chloramphenicol	Aplastic anaemia
Erythromycin estolate	Cholestatic hepatitis
Methyldopa	Hemolytic anemia
Oral contraceptives	Thromboembolism
Practolol	Sclerosing peritonitis
Reserpine	Depression
Statins	Rhabdomyolisis
Thalidomide	Congenital malformations

Source: WHO Policy Perspectives on Medicines: Pharmacovigilance-ensuring the safe use of medicines. Geneva: WHO, October 2004.

Adverse Drug Events (ADEs): Impact – Healthwise

- 4.2 – 30% of all hospital admissions: USA and CANADA; 5.7 – 18.8% in Australia; 2.5 – 10.6% in Europe[1]
- 2.1 – 5.2% hospitalisation in children; 39% in paediatric populations – life-threatening or fatal[2]
- USA: 11.4-35.5% of emergency department visits in older adults are due to drug-related causes[3]
- ADRs increase mean hospital stay: 8 to 20 days[4]
- ADRs increase mortality[4]
- USA: 5.3% admissions (2.2 million) and 100,000 deaths[5]

Estimates of drug reaction related admissions in Africa???

1 Howard RL et al. Br J Clin Pharmacol. 2007 Feb; 63(2):136-47
2 Impicciatore P et al. Br J Clin Pharmacol. 2001 Jul; 52(1):77-83
3 Budnitz DS et al. Ann Intern Med. 2007 Dec 4; 147(11):755-65
4 Davies EC et al. PLoS One. 2009; 4(2):e4439
5 J Ayub Med Coll Abbottabad 2015;27(3):702–6

Adverse Drug Events (ADEs): Impact - Economic

- USA: ADRs cost ~30.1-136 billion dollars annually[1,2]
- Preventable ADR more costly than non-preventable[3]
- Actual cost of ADRs in hospitalised patients: 2262 US dollars[4]
- Varying costs between wards: USD 13,994 (non-ICU) and USD 19,685 (ICU)[5]

Estimates of drug reaction related costs in Africa???

1 Kalisch LM et al. Aust Prescr. 2011;34:162–6
2 J Ayub Med Coll Abbottabad 2015;27(3):702–6
3 Bates DW et al. JAMA. 1997 Jan 22-29; 277(4):307-11.
4 Classen DC et al. JAMA. 1997 Jan 22-29; 277(4):301-6
5 Cullen DJ et al. Crit Care Med. 1997 Aug; 25(8):1289-97

Adverse Drug Reactions: Effect

MERCK News Release

Merck Agreement to Resolve U.S. VIOXX® Product Liability Lawsuits

Agreement Provides for $4.85 Billion Payment

The NEW ENGLAND JOURNAL of MEDICINE

Volume 351:1707-1709 October 21, 2004 Number 17 Next ▸

Failing the Public Health — Rofecoxib, Merck, and the FDA

Eric J. Topol, M.D.

Drugs Withdrawn from Market Due to Safety Issues

Astemizole Grepafloxacin Rezulin

Cisapride (Propulsid) Terfendine (Seldane)

Trovafloxacin Valdecoxib

Redux (dexfenfluramine) Pondimin (fenfluramine) Baycol

Pemoline Etretinate

Posicor (mibefradil) Nomifensine

Duract (bromfenac)

Ticrynafen Lotronex

Introduction to Pharmacovigilance

ispe International Society for Pharmacoepidemiology

UNAM

Outline

- What is Pharmacovigilance?
- Definitions of some terminologies used in Pharmacovigilance
- The role of Pharmacovigilance
- Overview of Risk Management Guidance
- Reporting and Collecting adverse events (AEs)

Pharmacovigilance, What is it?

"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. Encompasses the use of pharmacoepidemiological studies".

(ICH E2E)

Definitions: Pharmacoepidemiology

The study of the use and the effects of drugs in large numbers of people.

Strom BL, Pharmacoepidemiology. 5th Edition

Definitions: Adverse Event

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Source: ICH, *ICH Guideline, Clinical safety data management: definitions and standards for expedited reporting*, 1995.

Definitions: Adverse Drug Reaction

Adverse Drug Reaction (ADR): A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Event vs. Reaction

ADR and AE: are these terms synonymous, and so can be used interchangeably?

Event —Causality Assessment→ Reaction

…event which may not have a causal relationship with the pharmaceutical product

…a response to a drug, direct link established

The role of pharmacovigilance

Aim of Pharmacovigillance

- identifying adverse events and
- understanding their nature, frequency, and potential risk factors

Mechanism: closely monitor the use of pharmaceutical products

Objective: identification and evaluation of **safety signals** ➔ ➔ ➔ Prevention of ADR/ Patient Safety

Safety Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented[1]

Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events.[2]

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

A single event can be a signal

1. World Health Organization. Safety of medicines: a guide to detecting and reporting adverse drug reactions . Available from: http://whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf
2. Hauben, M. & Aronson J. Defining 'Signal' and its Subtypes in Pharmacovigilance Based on a Systematic Review of Previous Definitions. Drug Safety 2009; 32 (2): 99-110

Overview of Risk Management Guidance:

The emergence of Risk Evaluation Management Strategies (REMS)

Prescription Drug User Fee Act (PDUFA)

- PDUFA was a law passed by the US Congress in 1992
- FDA: collect fees ➔ fund the new drug approval process
- Funds were designated for use only in drug approval activities.
- **Result:** In the 1st 8-yrs increase the number of new drug reviewers by 77%,
- **Outcome:** the median approval time for non-priority drug by half from 27 months to 14 months.
- **Impact:** Resources for non-approval activities reduced

PDUFA III's Risk Management Guidance

Congress reauthorized PDUFA III in 2002.

One of the goals of PDUFA III was to provide guidance for industry on risk management activities

FDA issued three concept papers:

- Conducting premarketing risk assessment
- Developing and implementing risk minimization tools
- Performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments

FDA Amendments Act 2007

- FDA authorised to:
  - Inform applicants to submit and implement "risk evaluation and mitigation strategies" (REMS)
- REMS:
  - is a formal Risk Evaluation and Mitigation Strategy.
- Purpose of the REMS:
  - to generate evidence that shows that **BENEFIT** outweighs **RISK**

Elements of a REMS

- Timetable for submission of assessments of the REMS Strategy; Frequency may be increased or reduced as necessary
- Medication Guide
- Patient Package Insert
- Communication Plan to HCPs
- Requirements To Train/Educate Prescribers
- Certification of Pharmacies, Practitioners or Healthcare Facilities
- Restrictions on Distribution Sites
- Mandatory Lab Tests for Patients
- Other Required Monitoring or Registry.

Reporting and Collecting Adverse Events

Importance of Adverse Event Collection

Patient safety

Regulatory compliance

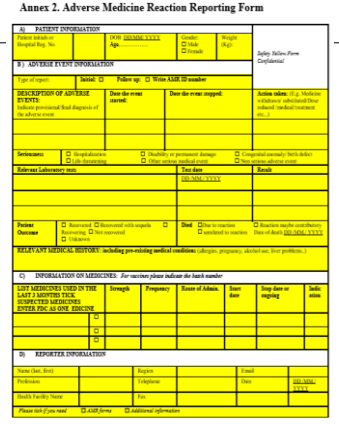
Product information (e.g., package insert)

Prescriber confidence

How Events are Reported

- Filling and posting/faxing the **safety yellow form** (TIPC, Namibia)
- Calling the pharmacovigilance centre
- FDA on-line report submission (MedWatch)
- Call the pharmaceutical company:
  - to report event,
  - to seek drug information*

Safety Yellow Form



Types of Adverse Event Reports

Clinical trial reports

AE reported from on-going clinical trails
- Required by regulator

Post-marketing study reports

AE reported from post-marketing study (i.e., Prescription Event Monitoring study; Retrospective Cohort studies)
- May be implemented on request by regulator Or by an interested researcher

Spontaneous reports

Reports from customers, HCPs, or Sale Reps
- Not required, mostly voluntary
- **Drug safety concerns** can arise from spontaneous reports

Establishment of ADRs Spontaneous Reporting Systems

1958 In **Germany**, Drug Commission of the German Medical Association (DCGMA) first requested all doctors to report adverse drug reactions to the Drug Commission

1962 **USA FDA** established the ADRs Spontaneous Reporting system known as Medwatch

1963 In **Australia**, Department of health and aging and Therapeutic Goods Administration established Blue Card system

1964 In **United Kingdom**, Medicines and Healthcare products Regulatory Agency (MHRA) and Commission on Human Medicines (CHM) established the Yellow Card system to collect ADRs.

1965 In **Canada**, Canadian Adverse Drug Reaction Monitoring Program（CADRMP）was established.

1968 In *1968*, **WHO** established Collaborating Center for International drug Monitoring：

Spontaneous Reporting Systems

WHO. UMC. http://www.who-umc.org

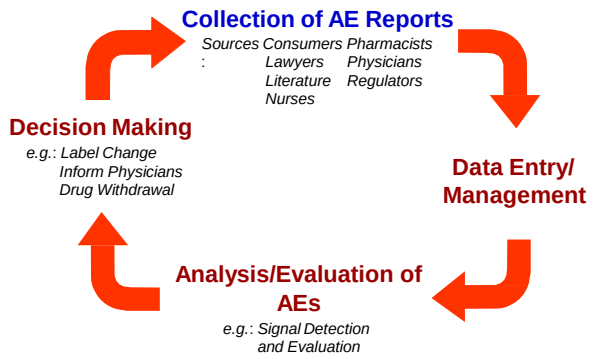
FDA U.S. http://www.fda.gov/medwatch

CADRMP, http://www.hc-sc.gc.ca/hpb-dgps/therapeut.

U.K. http://www.yellowcard.gov.uk/

TGA, http://www.tga.gov.au/adr/bluecard.htm#pdf

Spontaneous Reports: Initial node of the Pharmacovigilance Cycle



Factors Affecting Spontaneous Reporting

1. **Volume of drug use** (more use → more reports)
2. **Duration on the market** (newer drugs → higher reporting rate)
3. **Severity of event** (greater severity → higher reporting rate)
4. **Label status** (unlabeled events → higher reporting rate)
5. **Current trends** (recent years → higher reporting rate)
6. **Publicity** → higher reporting rate
7. **Manufacturers** (rates vary among manufacturers)

Strengths and limitations of Spontaneous Reports

Strengths

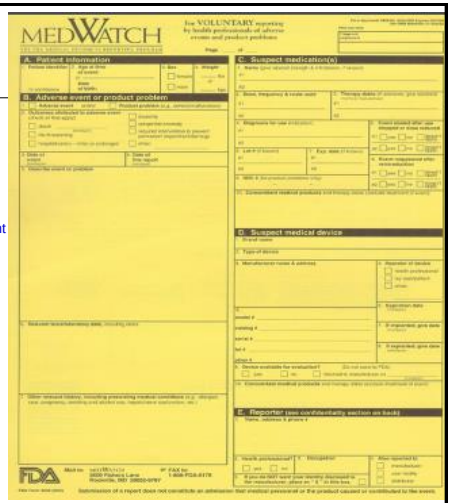
- Treatment of "real-world" population.
- Large sample size – potential to detect rare events.
- Cost
- Hypothesis generating

Limitations

- Passive surveillance
- Uncertainty that the suspect drug caused the event.
- Underreporting (numerator)
- Reporting bias
- No patient exposure data (denominator)
- No control group
- Latency of drug effect
- Inadequacy/incompleteness of reported information.

Content of AE Reports

Patient	Demographics – age, gender, race, etc. Pre-existing medical conditions
Event	Onset of event, event outcome, dechallenge and rechallenge
Product	Dosage (first dose, last dose), duration, concomitant medications
Reporter	Consumer, health professionals



Classification of ADR
Serious/Unexpected/Related

Serious

- Death
- Life-threatening
- Hospitalization
- Disability
- Congenital anomaly
- Other

Unexpected

- Any ADE or ADR, the nature or severity of which is not consistent with the applicable product information.
- i.e., not in the clinical investigator's brochure (CIB) or package insert (PI).

Related

- Assessed by HCPs

Type of Reporting Methods

15-Day Alert Reports

7-Day Alert Reports

Periodic Reporting

15-Day Alert Reports

Clinical Trials

- Serious
- Unexpected
- Possibly related (per investigator or company)

- **Must be postmarked within 15 calendar days of receipt of information**

Spontaneous Reports

- Serious
- Unexpected (local label)
- Possibly related (EU only)

- **Must be postmarked within 15 calendar days of receipt of information**

7-Day Alert Reports

Criteria for reports

- Clinical trial event reports
- Serious unexpected events
- Death or life-threatening

Action required

- Must be phoned or faxed to FDA within 7 days of initial or follow-up information

Drug Safety Monitoring in Namibia

Serious reactions
-15 calendar days

Any AE for new drugs (No Time restriction)

New drugs
-5 working days (7 days) for serious AE

Expedited Reporting Requirements by HCRs

All serious reactions must be reported on an expedited basis and not later than 15 calendar days from receipt of the minimum information required by any personnel of the HCR. For new chemical entities, HCRs should expedite the report of any AE; all serious AE reports for new chemical entities should be reported to TIPC within 5 working days of the receipt of such reports by the HCR.

A second company that entered into relationships with the manufacturer for the marketing of the suspected product should submit adverse reaction reports as soon as any personnel of the sponsor receives the minimum information. The time frame for regulatory submission should be no longer than 15 days from first receipt of the minimum information by the second company.

Serious suspected adverse reactions occurring in all post-registration studies of which the manufacturer is aware should be reported to the NMRC on an expedited basis.

Lack of efficacy of medicines used for the treatment of life-threatening diseases, vaccines and contraceptives should be considered as requiring expedited reports.

Periodic Reporting

Required as part of post marketing drug risk assessment program

To summarize interval safety data

To conduct systematic analyses of safety data on a regular basis

An opportunity to re-evaluate the benefits-risk ratio

Periodic Reporting (Cont'd)

Periodic Adverse Drug Experience Report (PADER)

- FDA report
- Quarterly for the first 3 years following drug's approval, then annually thereafter

Periodic Safety Update Report (PSUR)

- Worldwide report
- Biannual for the first 2 years following drug's approval, annually for 3 years, then every 5 years.

Drug Safety Monitoring in Namibia (2)

Frequency for PSUR:
Every 6 months for the first 2yrs then annually for 3 yrs

10.2. Periodic Safety Update Reports

The HCR should submit to the NMRC the records of all suspected adverse reactions in the form of a periodic safety update report. This should be done immediately upon request by NMRC or periodically. The time period for PSUR shall be every six months for the first two years of initial marketing and annually for the subsequent three years. Thereafter, the periodic safety update reports shall be submitted at three-yearly intervals. Three-yearly interval shall be applicable to all medicinal products regardless of their date of authorization. The HCRs are therefore obliged to submit a "null" report, if no AMR report is submitted to them in the specified period. Whenever requested by the NMRC, the HCR is obliged to submit a summary

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report on AMRs occurring in and outside Namibia and collaborate with the NMRC in the conduct of PASS when deemed necessary. The HCR may request amendment of the periods referred to above either at the time of submission of the application for marketing authorization or following the granting of the marketing authorization.

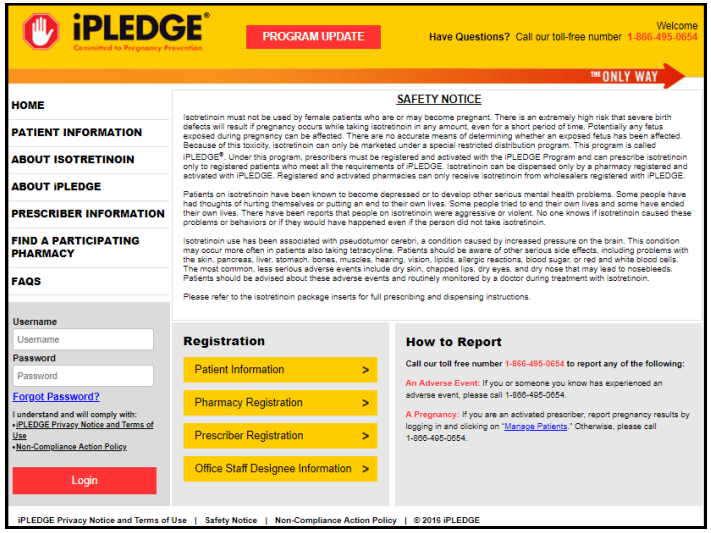
Results of Regulatory Reporting

Enhanced understanding of product's safety profile

- Labeling changes
- Dear Doctor/Pharmacist Letter
- Black Box Warning
- Restricted prescribing program
  - i.e. iPLEDGE program (Accutane)
  - 22,000 prescribers and 71,700 patients

Table 1 Important Events in the history of Accutane®

Years	What happened in this year	Measures
In 1982	Drug approved by FDA and launched in market	Approved as Pregnancy Category X; label warning about the pregnant women; Patient Information Brochure
In 1983	A first report of infant born with malformations	Label change, First 'Dear Doctor' Letter Second 'Dear Doctor' Letter
From 1984 to 1987	Cases continually reported	Labeling changes Third 'Dear Doctor' Letter Roche issued 'Dear Doctor' Letter
In 1988	Advisory Committee Meeting; Accutane Pregnancy Prevention Program(PPP) introduced by FDA and Roche	U.S FDA and the Roche developed the PPP aimed at increasing women's awareness of the teratogenicity of the drug and of the importance of preventing conception
From 1989 to 2001	Approximately 85 cases of congenital anomalies after exposure to Accutane reported to FDA; FDA first faced the pressure of requiring the national registry	FDA announces changes to the risk management program to prevent birth defects caused by Accutane®. Another new conception was called S.M.R.T (System to Manage Accutane Related Teratogenicity), which was designed to enhance the safe and appropriate use of Accutane by strengthening the existing Accutane Pregnancy Prevention Program (PPP), a comprehensive patient education program.
2002	PPP was modified to SMRT; Expiry of the patent exclusivity of Accutane; At the same time, label revised again;	Three generic form of the drug in the U.S market: Amnesteen (Nov,2003); Sotret (Dec, 2002) and Claravis (April,2003)
2004	FDA faced the renewed pressure.	



Thalidomide: A **Tragedy** in History

ispe International Society for Pharmacoepidemiology

UNAM

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

McBride WG (1962). Thalidomide and congenital abnormalities. Lancet 2:1358.

Outcome

Around *15,000* fetuses were damaged by thalidomide, of whom about *12,000* in 46 countries were born with birth defects, with only *8,000* of them surviving past the first year of life.

- Under the law at that time, FDA had 60 days to review a drug application. **Kelsey** had concerns about the drug from the beginning. The chronic toxicity studies were not long enough, the absorption and excretion data were inadequate, and the manufacturing controls had shortcomings.
- After Kelsey detailed these deficiencies in a letter to Richardson-Merrell, the company sent in additional information--but not enough to satisfy Kelsey.

  "The clinical reports were more on the nature of testimonials," says Kelsey, "rather than the results of well-designed, well-executed studies."
- Kelsey continued to request more data to show the drug's safety.
- Dr. Joseph Murray, Richardson-Merrell's representative, grew increasingly frustrated. He made repeated phone calls and personal visits to Kelsey, and complained to her superiors that she was **unreasonable and nit-picking, and that she was delaying the drug's approval unnecessarily**.

  "*Richardson-Merrell may have been over-eager, they were particularly disappointed because Christmas is apparently the season for sedatives.*"

Bren, Linda (March/April 2001). "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History". *FDA Consumer Magazine*. Http://www.fda.gov/fdac/features/2001/201_kelsey.html

- *In December of 1960,* three months after Richardson-Merrell submitted its application, the BMJ published a letter from a physician, Leslie Florence, who had prescribed thalidomide to his patients**.** Florence reported seeing cases of peripheral neuritis, a painful tingling of the arms and feet, in patients who had taken the drug over a long period of time.
- After reading the journal letter, Kelsey immediately contacted Richardson- Merrell, requesting further information on this serious side effect. She suspected that a drug that could damage nerves and could also affect a developing fetus. Her suspicions soon proved to be grimly accurate.

……..

- In March 1962, Richardson-Merrill withdrew its application from FDA.
- Richardson-Merrell had distributed more than 2.5 million thalidomide tablets to more than 1,000 doctors throughout the United States on what was called an *investigational basis*.
- In the US, there were only about 17 children born with thalidomide-associated deformities.

Kefauver-Harris Amendment (1962)

- In 1962, Food, Drug, and Cosmetics Act Amendments of 1962 were passed unanimously by Congress
- The Kefauver-Harris Amendment to the US Federal Food and Drugs Act, firstly required
  - premarketing submission of both ***efficacy and safety*** data to the Food and Drug Administration (FDA)
  - It also required that all antibiotics be certified, and gave FDA control over prescription drug advertising.
- FDA investigational Drug Branch evaluated proposal clinical trials for compliance with investigational drug regulations. **(Now, IND)**

Return of Thalidomide and REMS

- In 1998, FDA approved thalidomide under a **restricted access system**, for the treatment of erythema nodosum leprosum associated with leprosy (Hansen's disease).
- Because of thalidomide's teratogenicity, its distribution is closely regulated by the FDA and sponsor through the System for Thalidomide Education and Prescribing Safety (STEPS) program.
- In March,2008, FDA required the sponsor to develop a REMS to ensure the benefits outweigh the risk.

Lotronex (Alosetron) Withdrawal

- Approved in February 2000 for irritable bowel syndrome in women
- Events of ischemic colitis and severe constipation
- More than 70 cases of serious events (at least 49 cases of ischemic colitis)
  - 34 hospitalizations
  - 10 requiring surgery
  - At least 5 resulted in death
- Pulled from market in November 2000

Lotronex (Alosetron) Withdrawal

New FDA Subcommittee on Drug Safety and Risk Management

- Met on April 23, 2002 to discuss reintroducing Lotronex to the market
- First time ever for an advisory panel to recommend putting a banned drug back on the market
- Recommended it only for women with severe chronic diarrhea from a definitively diagnosed case of irritable bowel at half the initially approved dose

FDA Mandated Risk Management Program

- Limit to certified doctors who could reasonably diagnose the condition
- Educational program for RPh's, MD's and patients
- Implementation or a reporting system for adverse events
- Plan to evaluate the effectiveness of the risk management plan
- Report all cases of ischemic colitis and other bowel problems within 15 days
- Complete at least 8 different post-marketing studies

Summary

Safety information is collected throughout the development cycle of the drug.

Clinical trials cannot detect all potential safety aspects of a new drug.

Collecting AEs is critical to:

- Ensuring patient safety
- Understanding the clinical profile of a drug
- Maintaining regulatory compliance

Questions