Clinical Analysis of Adverse Drug Reactions

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Objectives

- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs
- Describe basic methods to detect, evaluate, and document ADRs
- FDA adverse drug reaction initiatives

Definition - WHO

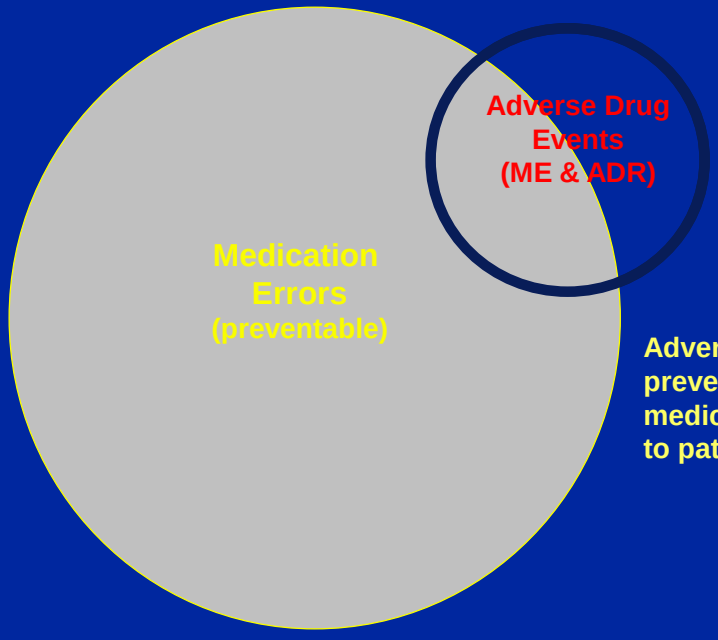
- WHO
  - response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function
  - Purposely excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

Definition - FDA

- Adverse drug reaction according to the U.S. Food and Drug Administration (FDA)
  - Any undesirable experience associated with the use of a medical product in a patient.

Adverse Drug Events

Adapted from Bates et al.



Adverse Drug Event: preventable or unpredicted medication event---with harm to patient

Pharmacovigilance

- The science of adverse drug reactions
- detection, assessment, understanding and prevention of adverse effects
- Regulatory agencies, pharmaceutical companies and individual healthcare providers enact a system

Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients*
- 6.7% incidence of serious ADRs*
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions

*JAMA. 1998;279:1200-1205.

Epidemiology

- 82% of American adults take at least one medication and 29% take five or more
- 700,000 emergency department visits and 120,000 hospitalizations are due to ADEs annually
- $3.5 billion is spent on extra medical costs of ADEs annually
- At least 40% of costs of ambulatory (non-hospital settings) ADEs are estimated to be *preventable*

http://www.cdc.gov/MedicationSafety/basics.html

Increase in Adverse Drug Events

- Development of new medications
- Discovery of new uses for older medications
- Aging American population
- Increase in the use of medications for disease prevention
- Increased coverage for prescription medications

http://www.cdc.gov/MedicationSafety/basics.html

Classification

- Onset
- Severity
- Type

Classification

- Onset of event:
  - Acute
    - within 60 minutes
    - Anaphylactic shock, bronchoconstriction
  - Sub-acute
    - 1 to 24 hours
    - Rash, serum sickness, abx associated colitis
  - Latent
    - > 2 days
    - Eczematous eruptions, tardive dyskinesia

Classification - Severity

Severity of reaction:

- **Mild**
  - » bothersome but requires no change in therapy
  - » Metallic taste with metronidazole
- **Moderate**
  - » requires change in therapy, additional treatment, hospitalization
  - » Amphotericin induced hypokalemia
- **Severe**
  - » disabling or life-threatening
  - » QT interval prolongation, kidney failure

Classification - Severity

- FDA Defines Serious ADR
  - Result in death
  - Life-threatening
  - Require hospitalization
  - Prolong hospitalization
  - Cause disability
  - Cause congenital anomalies
  - Require intervention to prevent permanent injury

Classification

Type A

- extension of pharmacologic effect
- often predictable and dose dependent
- responsible for at least two-thirds of ADRs
- e.g., propranolol and heart block, anticholinergics and dry mouth

Type B

- idiosyncratic or immunologic reactions
- rare and unpredictable
- e.g., chloramphenicol and aplastic anemia
- Rash caused by beta lactam antibiotics

IMMUNE REACTION	MECHANISM	CLINICAL MANIFESTATION	TIMING OF REACTION
Type I (IgE mediated)	Drug-IgE binding to mast cells, release of histamine, inflam mediators	Urticaria, angioedema, bronchospasm, pruritis	Minutes to hours after exposure
Type II (cytotoxic)	Specific IgG or IgM antibodies directed at drug-hapten coated cells	Hemolytic anemia, neutropenia, thrombocypenia	Variable
Type III (immune complex)	Tissue deposition of drug-antibody complexes with complement activation, inflam.	Serum sickness, fever, rash, arthralgias, lympadenopathy, urticaria, vasculitis	1-3 weeks after exposure
Type IV (delay hypersensitivity)	MHC presentation of drug molecules on T cells , cytokine and inflam. med. release	Allergic contact dermatitis, maculopapular rash	2 to 7 days after cutaneous drug exposure

Adapted from Am Fam Physician 2003;68:1782

Common Causes of ADRs

- Antibiotics
- Antineoplastics*
- Anticoagulants
- Cardiovascular drugs*
- Hypoglycemics
- Antihypertensives
- NSAID/Analgesics
- Diagnostic agents
- CNS drugs*

*account for 69% of fatal ADRs

Body Systems Commonly Involved

- Hematologic
- CNS
- Dermatologic/Allergic
- Metabolic
- Cardiovascular
- Gastrointestinal
- Renal/Genitourinary
- Respiratory
- Sensory

ADR Risk Factors

- Age (children and elderly)
- Multiple medications
- Multiple co-morbid conditions
- Inappropriate medication prescribing, use, or monitoring
- End-organ dysfunction
- Altered physiology
- Prior history of ADRs
- Extent (dose) and duration of exposure
- Genetic predisposition

ADR Detection

- Subjective report
  - patient complaint
- Objective report:
  - direct observation of event
  - abnormal findings
    - » physical exam
    - » laboratory test
    - » diagnostic procedure

ADR Detection

- Medication order screening
  - abrupt medication discontinuation
  - abrupt dosage reduction
  - orders for “tracer” or “trigger” substances
  - orders for special tests or serum drug concentrations
- Spontaneous reporting
- Medication utilization review
  - Computerized screening
  - Chart review and concurrent audits

ADR Detection in Clinical Trials

- **Methods**
  - **Standard laboratory tests**
  - **Diagnostic tests**
  - **Complete history and physical**
  - **Adverse drug event questionnaire**
    - » **Extensive checklist of symptoms categorized by body system**
    - » **Review-of-systems approach**
    - » **Qualitative and quantitative**

ADR Detection in Clinical Trials

Limitations

- exposure limited to few individuals
  - » rare and unusual ADRs not detected
  - » 3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty
- exposure is often short-term
  - » latent ADRs missed
- external validity
  - » may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

ADR Reporting in Clinical Trials
21 CFR 312

- Changes to safety information reporting during clinical trials starting March 2011
- Suspected adverse reaction – possibly, probably or definitely related to study agent
- Adverse reaction – *caused* by study agent

Preliminary Assessment

- **Preliminary description of event:**
  - **Who, what, when, where, how?**
  - ***Who*** **is involved?**
  - ***What*** **is the most likely causative agent?**
    - **Is this an exacerbation of a pre-existing condition?**
    - **Alternative explanations / differential diagnosis**
  - ***When*** **did the event take place?**
  - ***Where*** **did the event occur?**
  - ***How*** **has the event been managed thus far?**

Preliminary Assessment

- **Determination of urgency:**
  - **What is the patient's current clinical status?**
  - **How severe is the reaction?**
- **Appropriate triage:**
  - **Acute (ER, ICU, Poison Control)**

Detailed Description of Event

- History of present illness
- Signs / Symptoms:
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment,
  - Severity / extent, Site (location)
  - Temporal relationship (onset, duration, frequency)
  - Other associated signs and symptoms

Pertinent Patient/Disease Factors

- Demographics
  - age, race, ethnicity, gender, height, weight
- Medical history and physical exam
  - Concurrent conditions or special circumstances
    - » e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - Recent procedures or surgeries and any resultant complications
    - » e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

- End-organ function
- Review of systems
- Laboratory tests and diagnostics
- Social history
  - » tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
- Pertinent family history
- Nutritional status
  - » special diets, malnutrition, weight loss

Pertinent Medication Factors

- Medication history
  - Prescription medications
  - Non-prescription medications
  - Alternative and investigational therapies
  - Medication use within previous 6 months
  - Allergies or intolerances
  - History of medication reactions
  - Adherence to prescribed regimens
  - Cumulative medication dosages

Pertinent Medication Factors

- Medication
  - Indication, dose, diluent, volume
- Administration
  - Route, method, site, schedule, rate, duration
- Formulation
  - Pharmaceutical excipients
    - » e.g., colorings, flavorings, preservatives
  - Other components
    - » e.g., DEHP, latex

Pertinent Medication Factors

- Pharmacology
- Pharmacokinetics (LADME)
- Pharmacodynamics
- Adverse effect profiles
- Interactions
  - drug-drug
  - drug-nutrient
  - drug-lab test interference
- Cross-allergenicity or cross-reactivity

ADR Information

- Incidence and prevalence
- Mechanism and pathogenesis
- Clinical presentation and diagnosis
- Time course
- Dose relationship
- Reversibility
- Cross-reactivity/Cross-allergenicity
- Treatment and prognosis

ADR Information Resources

- Tertiary
  - » Reference books
    - – Medical and pharmacotherapy textbooks
    - – Package inserts, PDR, AHFS, USPDI
    - – Specialized ADR resources
      - Meyler's Side Effects of Drugs
      - Textbook of Adverse Drug Reactions
    - – Drug interactions resources
    - – Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)
  - » Review articles

ADR Information Resources

- Secondary
  - MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)
  - Excerpta Medica's Embase
  - International Pharmaceutical Abstracts
  - Current Contents
  - Biological Abstracts (Biosis)
  - Science Citation Index
  - Clin-Alert and Reaction
  - Scopus

ADR Information Resources

- Primary
  - » Spontaneous reports or unpublished data
    - – FDA
    - – Manufacturer
  - » Anecdotal and descriptive reports
    - – Case reports, case series
  - » Observational studies
    - – Case-control, cross-sectional, cohort
  - » Experimental and other studies
    - – Clinical trials
    - – Meta-analyses

Causality Assessment

- Prior reports of reaction
- Temporal relationship
- De-challenge
- Re-challenge
- Dose-response relationship
- Alternative etiologies
- Objective confirmation
- Past history of reaction to same or similar medication

Causality Assessment

- Examples of causality algorithms
  - Kramer
  - Naranjo and Jones
- Causality outcomes
  - Highly probable
  - Probable
  - Possible
  - Doubtful

Naranjo ADR Probability Scale

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

		Yes	No	Do Not Know	Score
1.	Are there previous *conclusive* reports on this reaction?	+1	0	0	1
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	1
4.	Did the adverse reactions appear when the drug was readministered?	+2	-1	0	0
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	1
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	1
				Total Score	8

Total Score	*ADR Probability Classification*
9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Management Options

- **Discontinue the offending agent if:**
  - it can be safely stopped
  - the event is life-threatening or intolerable
  - there is a reasonable alternative
  - continuing the medication will further exacerbate the patient's condition
- **Continue the medication (modified as needed) if:**
  - it is medically necessary
  - there is no reasonable alternative
  - the problem is mild and will resolve with time

Management Options

- Discontinue non-essential medications
- Administer appropriate treatment
  - » e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon
- Provide supportive or palliative care
  - » e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
- Consider rechallenge or desensitization

Follow-up and Re-evaluation

- Patient's progress
- Course of event
- Delayed reactions
- Response to treatment
- Specific monitoring parameters

Reporting ADRs

Reportable

- All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related

Reporting ADRs

Reportable

- Hypersensitivity
- Life-threatening
- Cause disability
- Idiosyncratic
- Secondary to Drug interactions
- Unexpected detrimental effect
- Drug intolerance
- Any ADR with investigational drug

Documentation and Reporting

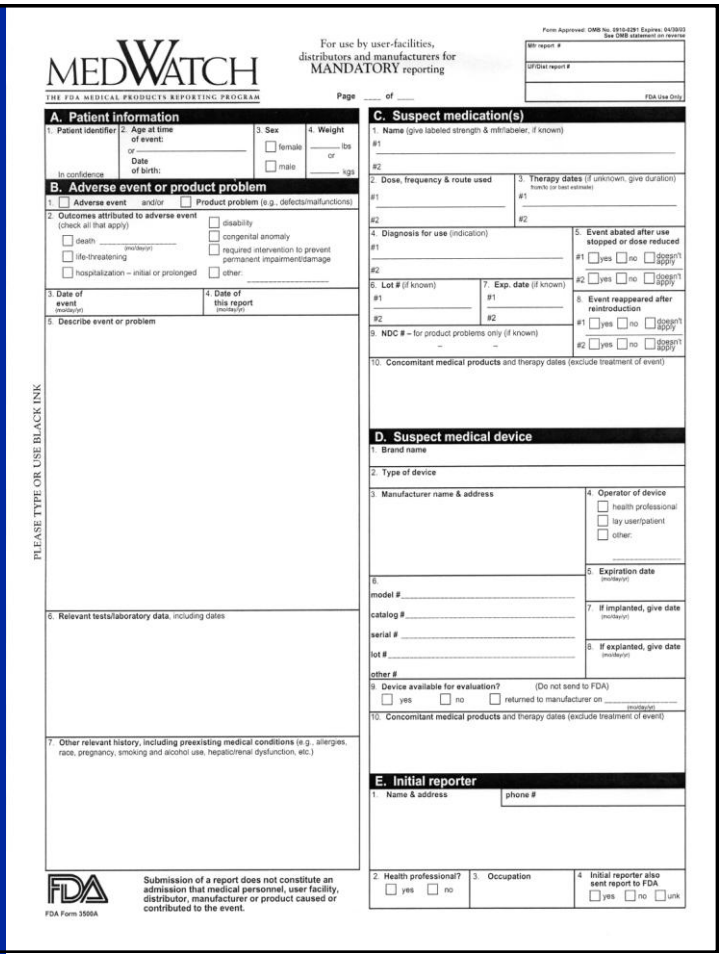
- Medical record
  - Description
  - Management
  - Outcome
- Reporting responsibility
  - JCAHO-mandated reporting programs
  - Food and Drug Administration
    - » post-marketing surveillance
    - » particular interest in serious reactions involving new chemical entities
  - Pharmaceutical manufacturers
  - Publishing in the medical literature

Components of an ADR Report

- Product name and manufacturer
- Patient demographics
- Description of adverse event and outcome
- Date of onset
- Drug start and stop dates/times
- Dose, frequency, and method
- Relevant lab test results or other objective evidence
- De-challenge and re-challenge information
- Confounding variables

MEDWATCH 3500A Reporting Form

https://www.accessdata.fda.gov/scripts/medwatch



MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse.

Mfr report #

UF/D/Ist report #

FDA Use Only

Page ____ of ____

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: / or Date of birth:
3. Sex — female / male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death (mo/day/yr)
   - life-threatening
   - hospitalization – initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 #2
2. Dose, frequency & route used #1 #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 #2
4. Diagnosis for use (indication) #1 #2
5. Event abated after use stopped or dose reduced #1 yes no doesn't apply #2 yes no doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction #1 yes no doesn't apply #2 yes no doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device: health professional / lay user/patient / other:
5. Expiration date (mo/day/yr)
6. model # / catalog # / serial # / lot # / other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? yes no returned to manufacturer on (mo/day/yr) (Do not send to FDA)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

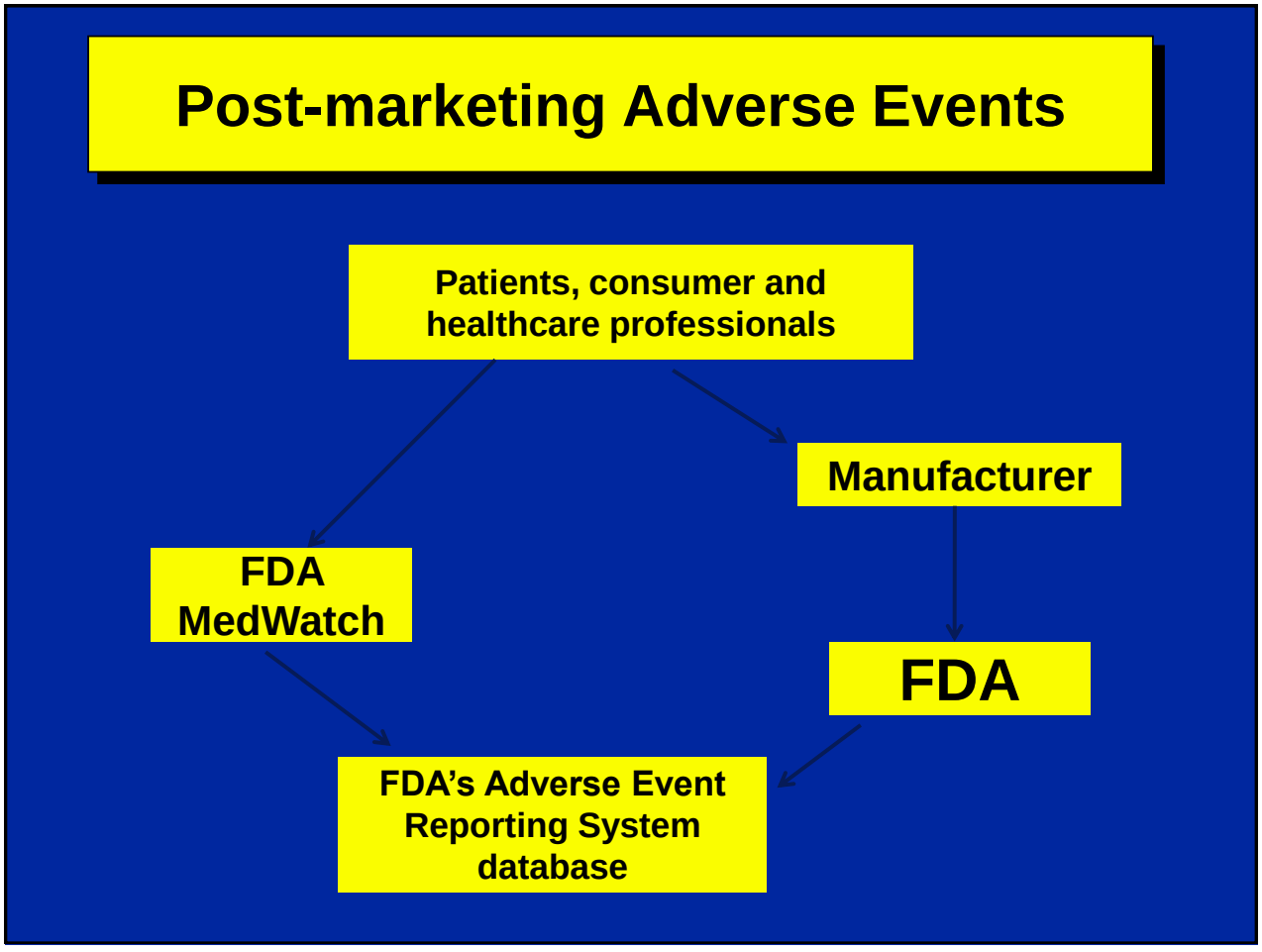
1. Name & address / phone #
2. Health professional? yes no
3. Occupation
4. Initial reporter also sent report to FDA yes no unk

FDA Form 3500A

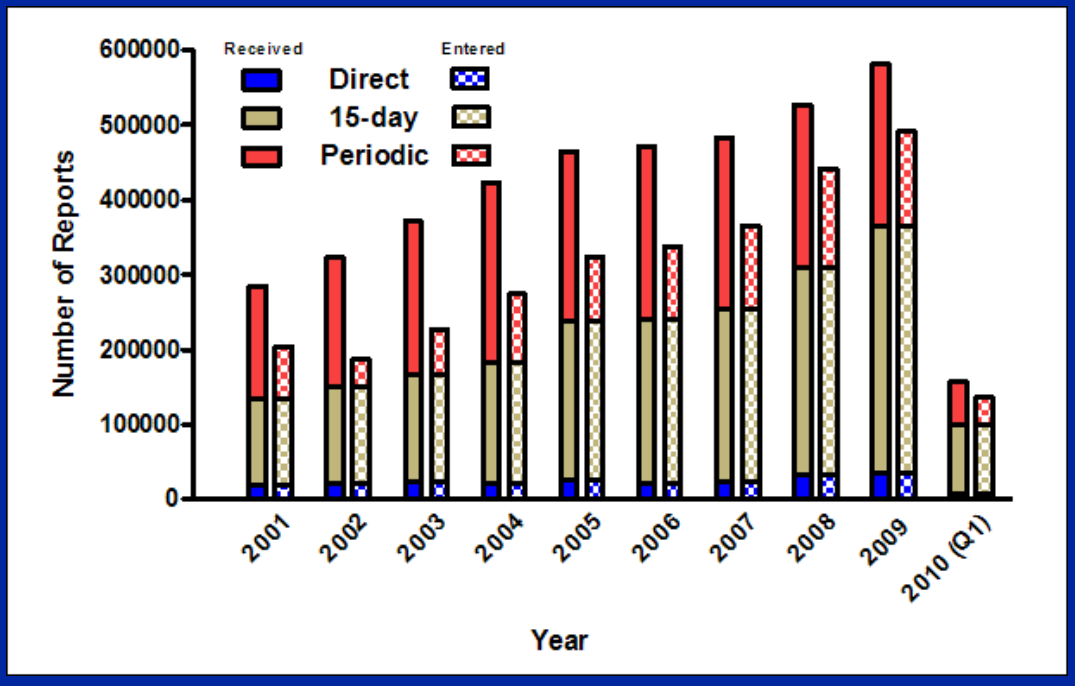
Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MedWatch Direct Reports

- Reports submitted directly to FDA through MedWatch by
  - Internet – on line reporting form
  - Mail or Fax
  - Telephone 1-800-FDA-1088


Post-marketing Adverse Events
Patients, consumer and healthcare professionals
Manufacturer
FDA MedWatch
FDA
FDA's Adverse Event Reporting System database

Reports Received and Reports Entered into AERS by Year



ISMP – QuarterWatch™ 2010 Quarter 2

- Analyzed computer excerpts from 33,068 reports
- Continued increase in reports – up 12% compared to Q2 2009
- Reports from manufacturers increased 24%
- Reports from consumers and health care professionals were 25% fewer

ISMP – QuarterWatch™ 2010 Quarter 2

Table 1. Selected Drug Safety Signals 2010 Quarter 2

Drug Names	Brand Names*	Adverse Effect	Cases	PRR#**	P Value
fenta**NYL**	**DURAGESIC**	Maladministrations	447	12.6	< 0.01
QUEtiapine	**SEROQUEL**	Diabetes	191	16.5	< 0.01
in**FLIX**imab	**REMICADE**	Skin cancers	154	101.3	< 0.01
alendronate	**FOSAMAX**	Lower limb fracture	126	50.4	< 0.01
exenatide	**BYETTA**	Inflammation of pancreas	118	32.5	< 0.01

** May have other names ** Proportional reporting ratio*

FDA Drug Safety Communications

- FDA provides easy access to important drug safety information
- Risk of Progressive Multifocal Leukoencephalopathy (PML) with the use of Tysabri (natalizumab) and increases with number of infusions
  - 31 confirmed cases of PML received by the FDA as of January 21, 2010
  - Additional information for patients and prescribers provided on website
  - This information will be included on the drug label and patient *Medication Guide*
  - Limited distribution prescribing system is in place

Risk Evaluation and Mitigation Strategy (REMS)

- Risk management plan that utilizes strategies that go beyond professional labeling to ensure drug benefits outweigh risks
- The FDA Amendments Act of 2007 (FDAAA) granted the FDA the authority to require the submission and implementation of a REMS
- REMS are designed to meet specific serious risk mitigation goals

REMS Considerations

- Does the product fill a significant unmet need?
- What is the magnitude of the risk?
- Do the data suggest ways to mitigate the risk?

REMS Components

- Medication Guide for patients
- Communication Plan for healthcare professionals
- Elements to Assure Safe Use (previously “restricted distribution”)
- Implementation system

Medication Guide Requirement

- Patient labeling could help prevent serious adverse events
- The product has serious risks that could affect a patient's decision
- Patient adherence to directions is crucial to product effectiveness

Communication Plan

- If FDA determines a communication plan is needed, it can include:
  - Letters to healthcare providers
  - Disseminating information through professional societies about serious risk of the drug and any elements to assure safe use

Elements to Assure Safe Use

- Prescriber training or certification
- Certification of dispensers
- Drug administration limited to certain health care settings
- Documentation of safe use prior to dispensing
- Required monitoring of patients
- Enrollment of patients in a registry

REMS Example
Victoza® (Liraglutide)

- Goal is to inform providers of the risk of acute pancreatitis (including necrotizing pancreatitis) and potential risk of medullary thyroid carcinoma
- Medication guide will be dispensed with each prescription
- Communication Plan
  - Dear doctor letter
  - Direct mail letter each year x 3 yrs
  - Highlighted information for prescribers will be distributed by manufacturer representatives

Sample of Victoza® Medication Guide

- Before taking Victoza, tell your healthcare provider if you have had:
- **pancreatitis**
- **stones in your gallbladder (gallstones)**
- **a history of alcoholism**
- **high blood triglyceride levels**
  - **These medical conditions can make you more likely to get pancreatitis in general. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking Victoza.**
- While taking Victoza:
- **Stop taking Victoza and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.**

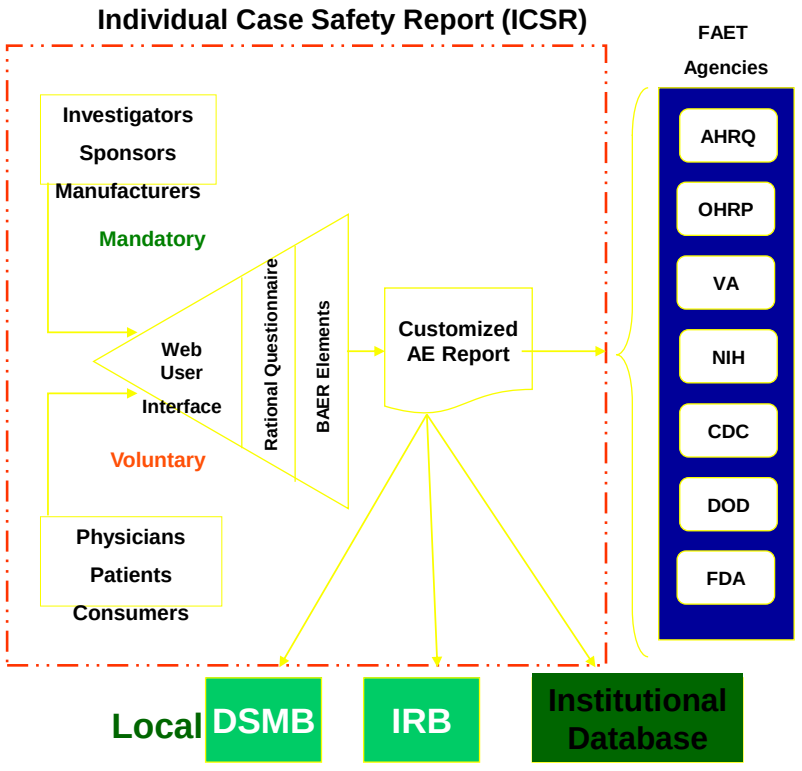
How to get FDA Drug Safety Alerts

- FDA Drug Safety Newsletter
  - http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/default.htm
- MedWatch Safety Alerts
  - http://www.fda.gov/Safety/MedWatch/ucm168422.htm
- FDA Patient Safety News
  - Video news show for health professionals
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/index.cfm

Future

- I-phone apps for MedWatch
- Hospital systems to report adrs directly to FDA
- FAERS – FDA Adverse Event Reporting System (enhanced analysis)
- Standardization of reporting to include data from Japan and Europe
- Federal Adverse Event Task Force (FAET)
- Innovative ways to increase reporting and identification of adverse drug reactions

Federal Adverse Event Reporting Portal



Slide courtesy of Office of Science Policy, Office of the Director, NIH

Safety Reporting Portal

- Launched in May of 2010, testing phase
- FDA safety issues involving:
  Human or animal reportable foods
  - Animal drugs
  - Pet foods
- NIH safety issues involving:
  NIH gene-transfer research


Portal Web Site
Safety Reporting Portal
HOME
ABOUT THE PORTAL
SAFETY REPORT DIRECTORY
FAQS
RELATED LINKS
CONTACT US
The Safety Reporting Portal
The Safety Report Portal streamlines the process of reporting product safety issues to the Food & Drug Administration (FDA) and the National Institutes of Health (NIH).
Whatever your role, (manufacturer, health care professional, researcher, public health professional, or concerned citizen), when you submit a safety report through this Portal, you make a vital contribution to the safety of America's food supply, medicines, and other products that touch us all.
Three Ways to Start
Save a report & finish later
See a list of your reports
Easier follow up
Create Account
Not ready to create an account but would like to submit a report? You can do that here.
Report as Guest
EMAIL
DrX@universitymedctr.
PASSWORD
Log In
Forgot password?
Remember me
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.
Learn more about mandatory and voluntary reporting.
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.
USA.gov
FDA U.S. Food and Drug Administration
NATIONAL INSTITUTES OF HEALTH
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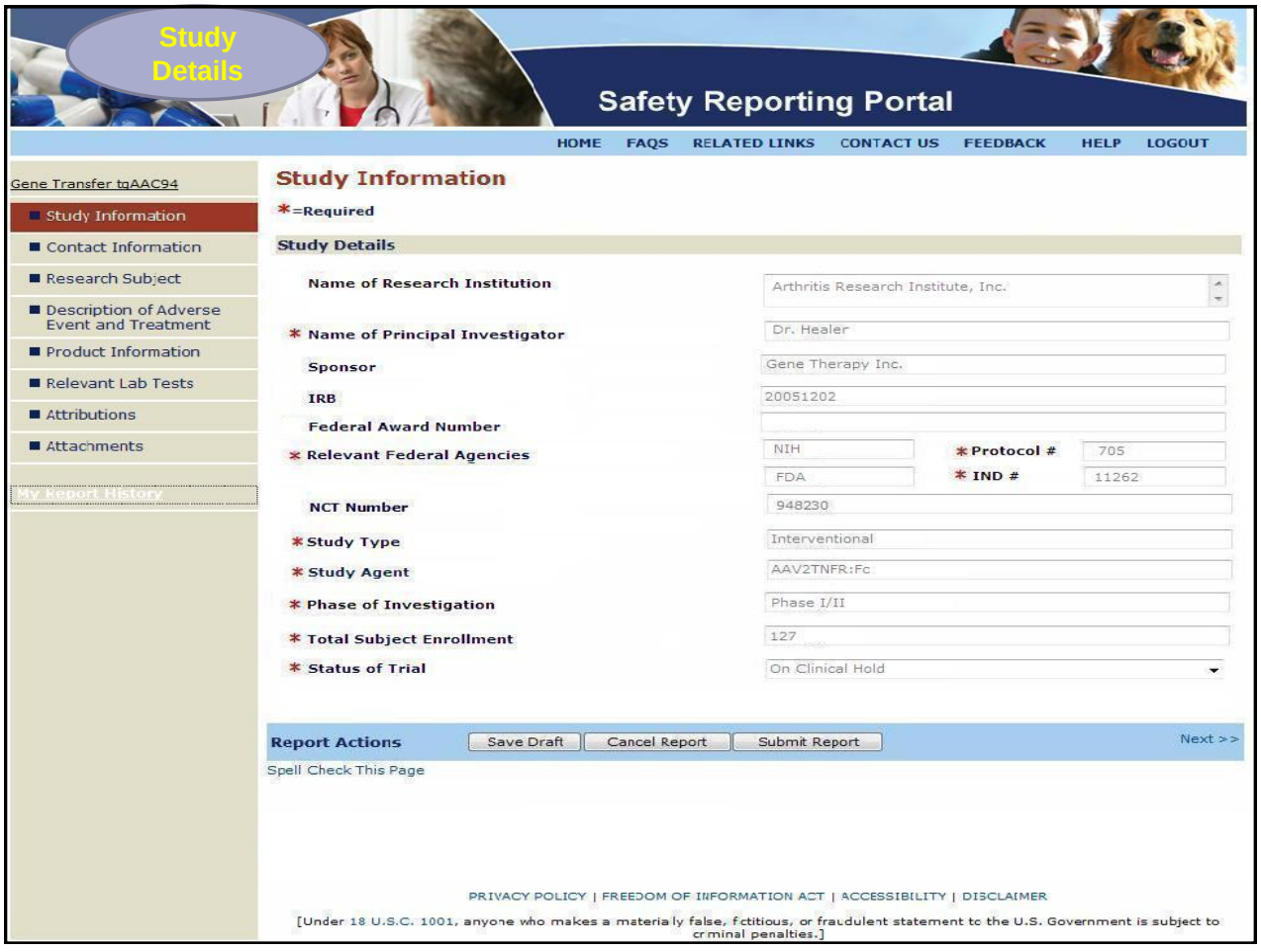
[Under 18 U.S.C. 1001, anyone who makes a materially false, fictitious, or fraudulent statement to the U.S. Government is subject to criminal penalties.]


Study Details
Safety Reporting Portal
HOME FAQS RELATED LINKS CONTACT US FEEDBACK HELP LOGOUT
Gene Transfer tgAAC94
Study Information
Contact Information
Research Subject
Description of Adverse Event and Treatment
Product Information
Relevant Lab Tests
Attributions
Attachments
Study Information
*=Required
Study Details
Name of Research Institution
Arthritis Research Institute, Inc.
* Name of Principal Investigator
Dr. Healer
Sponsor
Gene Therapy Inc.
IRB
20051202
Federal Award Number
* Relevant Federal Agencies
NIH
* Protocol #
705
FDA
* IND #
11262
NCT Number
948230
* Study Type
Interventional
* Study Agent
AAV2TNFR:Fc
* Phase of Investigation
Phase I/II
* Total Subject Enrollment
127
* Status of Trial
On Clinical Hold
Report Actions
Save Draft
Cancel Report
Submit Report
Next >>
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Questions ???