The Emerging Science of Drug Safety

Janet Woodcock M.D.
Director, Center for Drug Evaluation and Research, FDA
November 20, 2008

Drug Safety is in the News

- **Vioxx and other drug withdrawals**
- **New safety issues:**
  - **Avandia and cardiovascular risk**
  - **SSRIs and suicidality**
- **Heparin contamination**
- **Patients and prescribers often lack information about these safety controversies**
- **Decreased confidence in pharmaceuticals and in FDA review process**

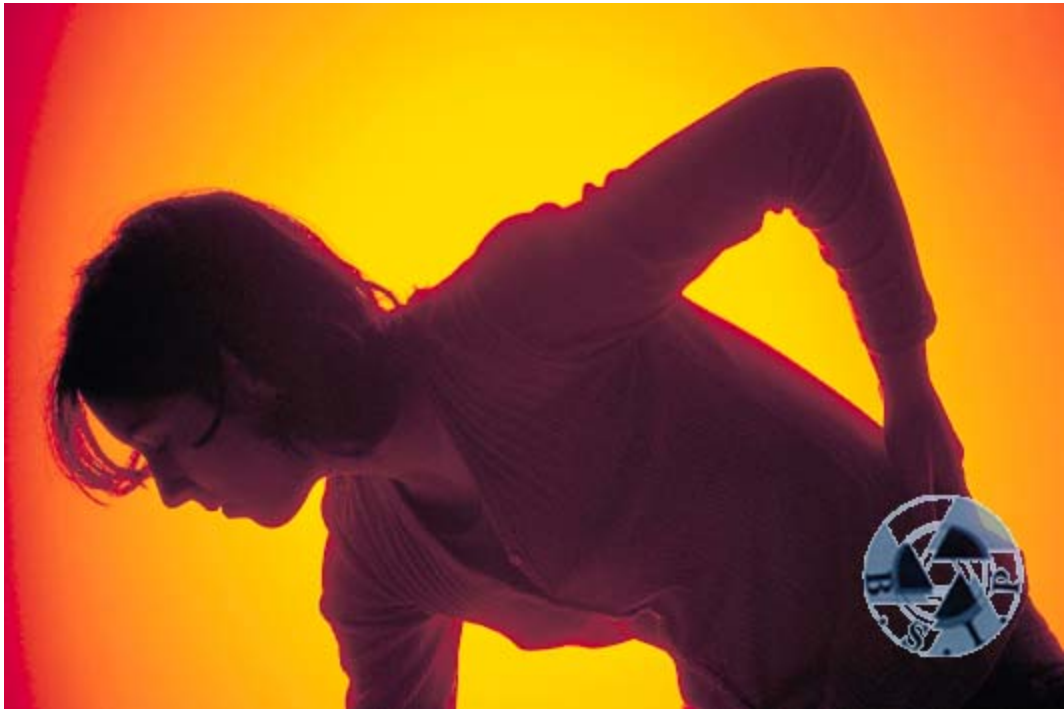
Are Drugs Safe?

- **No**
- **All drugs have risks, many are serious**
- **Drugs are approved because their benefits are deemed to outweigh their risks**
- **This is why, generally, only health professionals can prescribe drugs**
- **Even OTC drugs have risks, although they are fairly rare**

Why the Increase in Societal Concern?

- **Many more people rely on medicines to maintain health**
- **We understand more about the risks than we used to: ignorance was “bliss”**
- **Drug advertising has given the broad population exposure to the previously more closed world of medications and, possibly, has given an impression of greater safety than actually exists**


Dorothy Hamill
VIOXX®
(rofecoxib)
Ask your doctor
or other healthcare professional.
Available only by prescription.
For more information on VIOXX
from Merck, call 1-888-VIOXX-11.
VIOXX is a registered trademark of Merck & Co., Inc.
MERCK
© 2002 Merck & Co., Inc. All rights reserved. 20204727(1)-VIO-CON



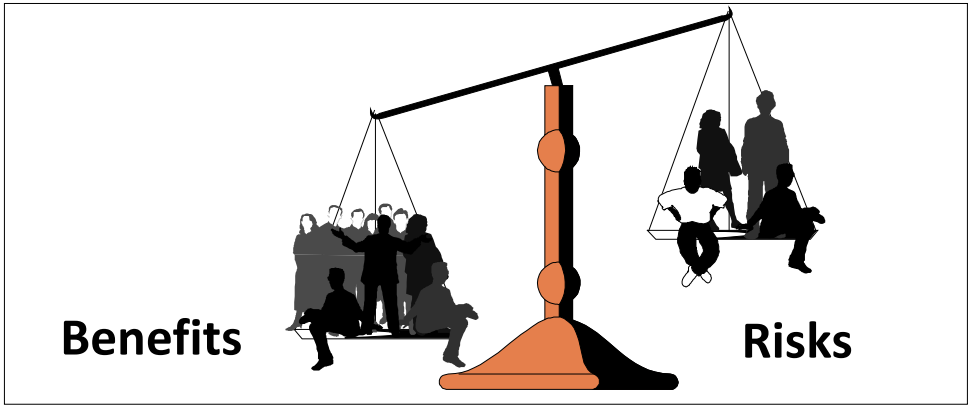

osteoarthritis, the most common type of arthritis.
ONE PILL—ALL DAY AND ALL NIGHT RELIEF.
You take VIOXX only once a day. Just one little pill can relieve your pain all day and all night for a full 24 hours.
VIOXX EFFECTIVELY REDUCED PAIN AND STIFFNESS.
In clinical studies, once-daily VIOXX effectively reduced pain and stiffness. So VIOXX can help make it easier for you to do the things you want to do. Like bending down to build sand castles with your child.
TAKE WITH OR WITHOUT FOOD.
VIOXX doesn't need to be taken with food. So, you don't have to worry about scheduling VIOXX around meals.
allergic reactions, such as asthma, to aspirin or other arthritis medicines should not take VIOXX.
Tell your doctor if you have liver or kidney problems, or are pregnant. Also, VIOXX should not be used by women in late pregnancy.
VIOXX has been extensively studied in large clinical trials. Commonly reported side effects included upper respiratory infection, diarrhea, nausea and high blood pressure. Report any unusual symptoms to your doctor.
ASK YOUR DOCTOR OR HEALTHCARE PROFESSIONAL ABOUT VIOXX.
Call 1-800-350-9799 for more information, or visit www.vioxx.com. Please see important additional information on the next page.
ONCE DAILY
VIOXX®

How Does Our Society Manage the Risks of Drugs?

- **FDA controls market access, content of label and regulates promotion—i.e., FDA regulates the industry**
- **Various bodies regulate or set requirements for health care facilities**
- **State licensing boards oversee pharmacists, physicians and other health professionals**

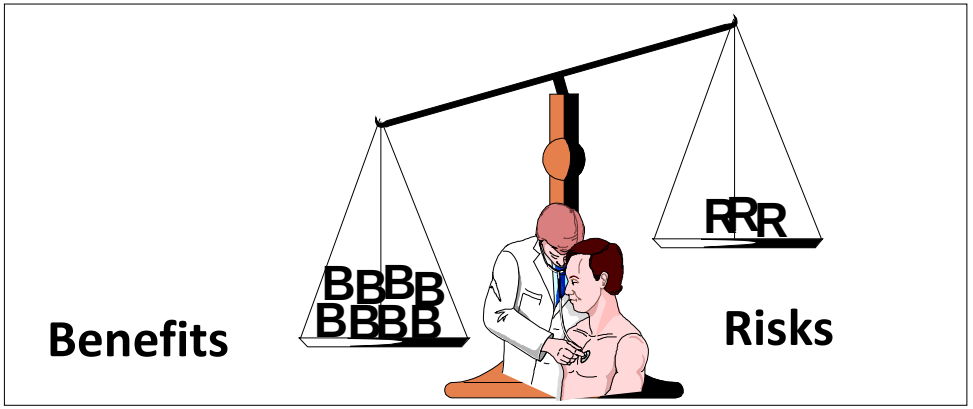
FDA

evaluates
benefits/risks
for the population



Provider

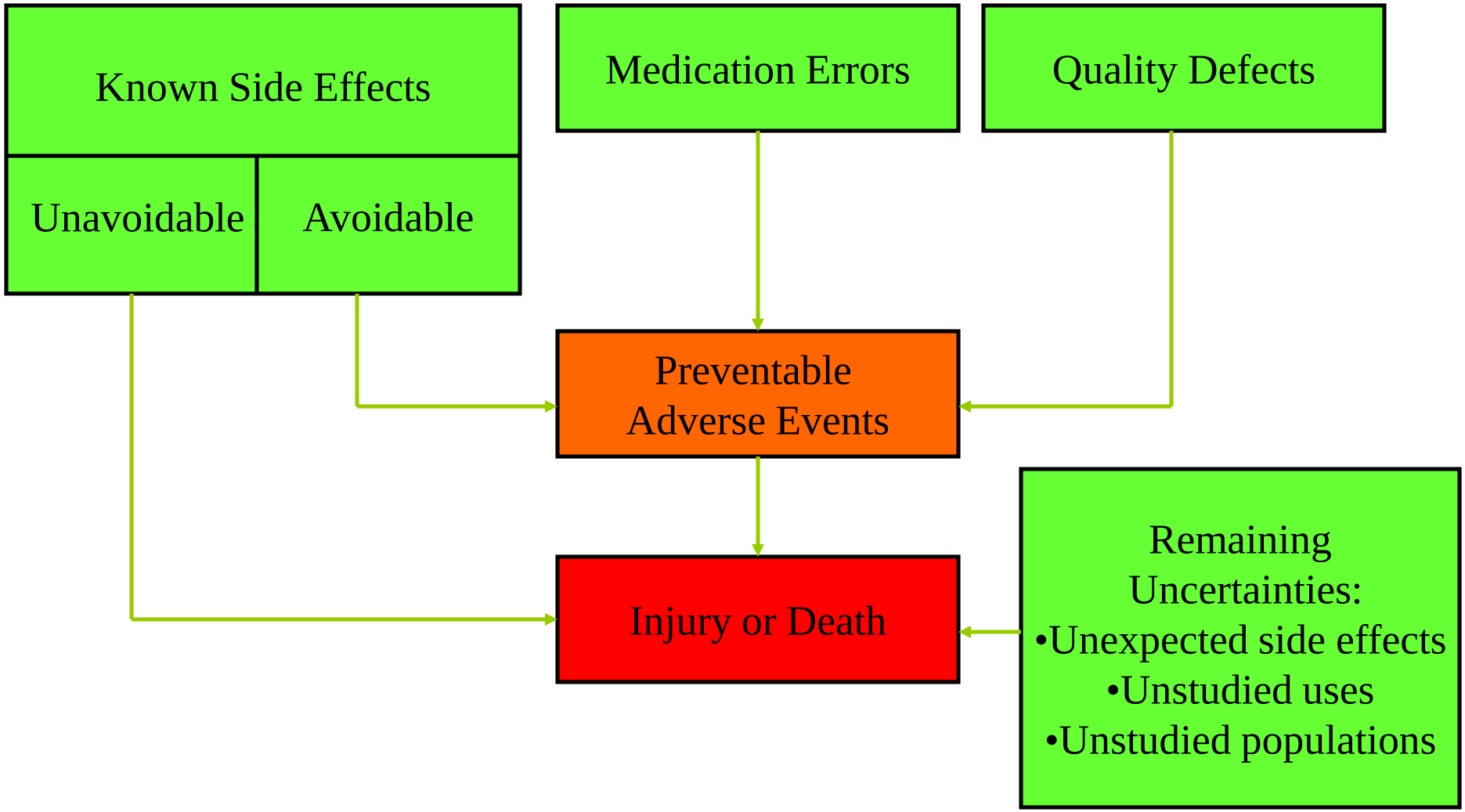
evaluates
benefits/risks
for a patient

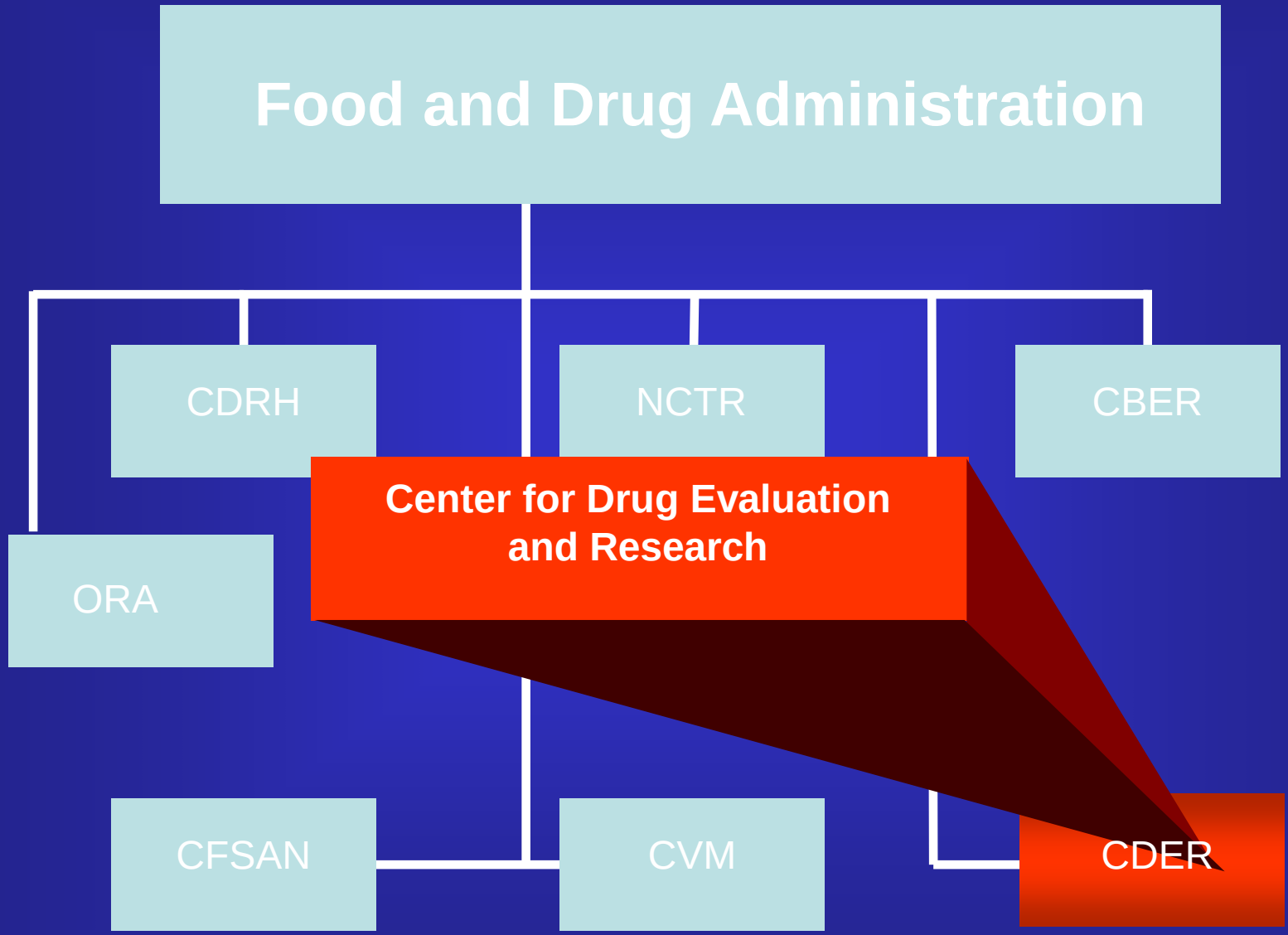


Patient

evaluates
benefits/risks
in terms of
personal values

Sources of Risk From Drugs




Food and Drug Administration
CDRH
NCTR
CBER
Center for Drug Evaluation and Research
ORA
CFSAN
CVM
CDER

FDA's Center for Drugs

Mission:

The Center for Drug Evaluation and Research (CDER) assures that safe and effective drugs are available to the American people.

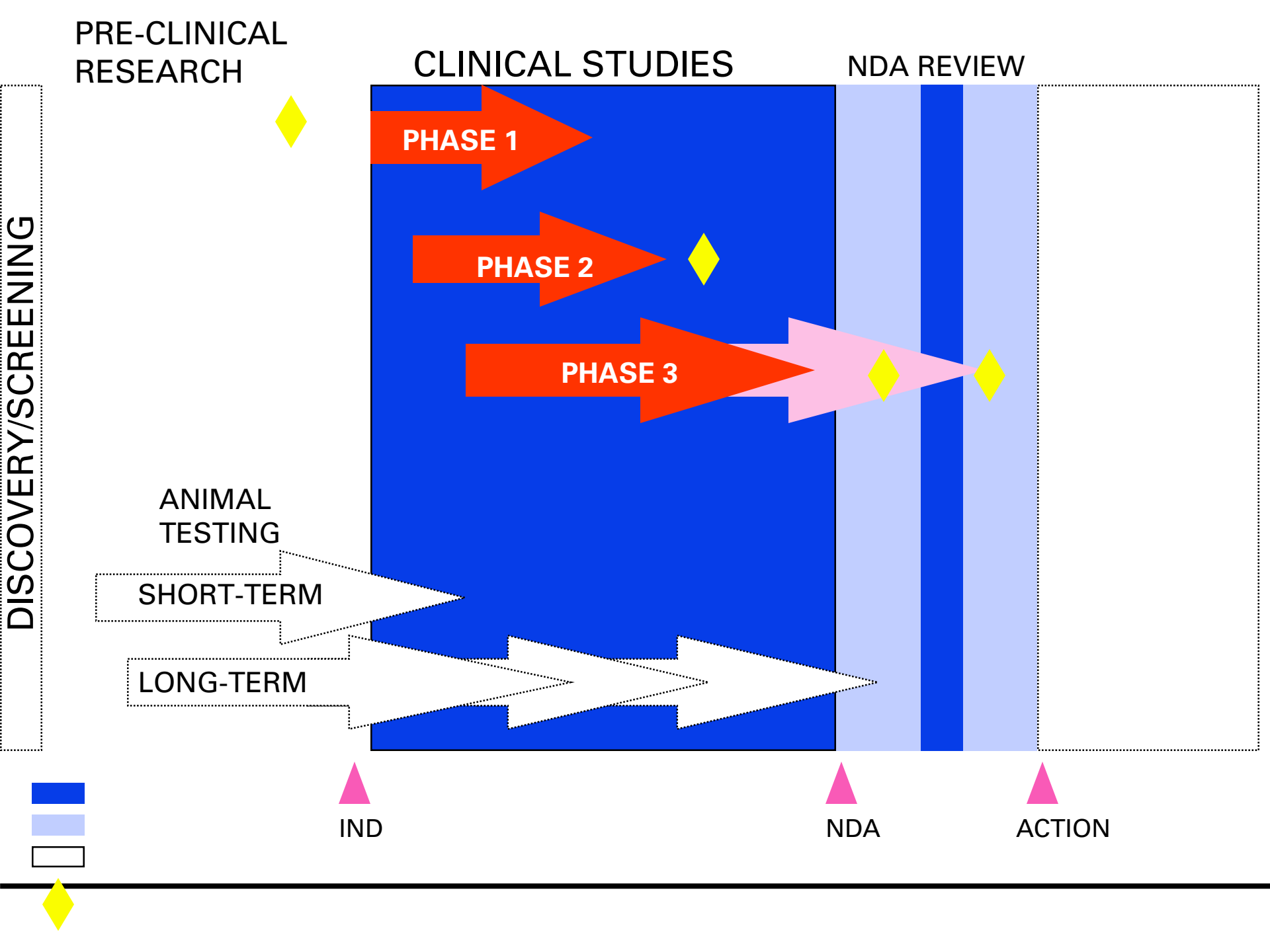
- **Makes Beneficial Drugs Quickly Available**
- **Keeps Dangerous Drugs Off The Market**
- **Improves Health For Americans**

CDER Multidisciplinary Review Team

- Pharmacists
- Physicians
- Chemists and investigators
- Statisticians
- Pharmacologists
- Microbiologists
- Pharmacokineticists
- Epidemiologists
- Safety evaluators

Managing the Risks of Drugs: The Current FDA System

- **Extensive evaluation of safety BEFORE marketing**
  - **Series of in vitro and animal tests before first-in-human testing begins**
    - **Safe animal dosing: human dosing starts 10-fold lower**
  - **Safety evaluation in clinical development**
- **Drug safety surveillance AFTER marketing**
  - **Spontaneous reports from healthcare system**
  - **Formal evaluation: clinical trials, population-based studies, registries**


PRE-CLINICAL
RESEARCH
CLINICAL STUDIES
NDA REVIEW
DISCOVERY/SCREENING
PHASE 1
PHASE 2
PHASE 3
ANIMAL
TESTING
SHORT-TERM
LONG-TERM
IND
NDA
ACTION

Safety Assessment BEFORE Marketing: How Much is Learned?

- **Traditionally, the clinical safety evaluation has been a "side effect" of the efficacy evaluation**
- **Clinical safety evaluation extrapolates from what is observed in clinical trials of efficacy—in other words, no formal trials investigating safety are done**
- **Despite costs of up to $1B, development programs not able to predict drug safety profile when marketed: great uncertainty remains**
- **Result: drug withdrawals, label changes, patient alarm**
- **Problem: these evaluations are all observational/empirical**

The New Safety Science: New Molecular Science and New Technologies Will Help Reduce Uncertainty

- **Better understanding/prediction of off-target effects**
- **Computer models of drug effects**
- **Pharmacogenomics**
- **Greater attention to drug metabolism and related pathways**
  - **Sometimes huge exposure differences with drug metabolizing enzyme variations**

Better Understanding of Off-Target Effects

- **Traditionally, drug discovery is based on "target" effects, i.e., potential benefit**
- **New methods can look at what OTHER effects the drug candidate might have**
  - **Screening candidates for effects on other "drug-able" targets in a library**
  - **Receptor binding studies**
  - **Use of cell based assays to understand effects on interactions**
  - **Cellular gene expression assays**

Use of New Technology

- **Computer-based Structure Activity Relationships (SAR)**
  - **FDA models for reproductive toxicity**
  - **FDA models for other toxicities based on animal and clinical outcomes**
- **Companies now screen candidate molecules to eliminate potentially toxic motifs**
- **Putting more gene expression, animal and clinical data into these systems will improve their predictive power**

New Safety Biomarkers

- **Public-private partnerships are identifying better markers of drug-induced toxicity**
  - **Drug-induced renal toxicity**
    - **Panel of new kidney injury markers has received approval from FDA and EMEA for use in animal studies**
    - **Human studies now being designed**
    - **Hope to have more sensitive makers for clinical use**

Safety Pharmacogenomics

- **Why do some people get a side effect and most don't?**
- **Sometimes there is a significant genetic contribution to the risk**
- **This can be tested for!**
  - **Warfarin: 50% of dose variation explained by genetic factors**
  - **Abacavir: HLA-B5701 confers risk for hypersensitivity reaction**
  - **Carbamazepine: HLA allele confers risk for Stevens-Johnson syndrome in Asians**
  - **Slow or non-metabolizers of drugs**

Other Trends in Safety Evaluation During Drug Development

- **Formal evaluation for specific drug toxicities:**
  - **QT Interval prolongation studies**
  - **Recent recommendation of endocrine advisory committee that some evaluation of cardiovascular toxicity of new diabetes therapies be carried out or started prior to approval**

- **Meta-analyses of clinical databases**
  - **Driven by reality that efficacy trials may not be adequately powered to detect less-common but serious toxicities**
  - **Particularly if toxicity is increase in frequency of relatively common problem**
  - **Many methodologic issues with doing this**

Example of a meta-analysis of clinical trials:
Atypical antipsychotics and death in patients with dementia

Trials: 15
randomized, parallel-group, placebo-controlled trials of aripiprazole, olanzapine, quetiapine and risperidone in patients with Alzheimer disease or other dementia.

Study Population:
3353 drug-treated patients and 1757 placebo-treated patients

Outcomes:
Dropouts and deaths

Analysis:
Odds ratios and risk differences based on patients randomized and relative risk based on total exposure to treatment

Source: Schneider et al. JAMA 2005;294:1934-1943

Example of a meta-analysis of clinical trials:
Atypical antipsychotics and death in patients with dementia

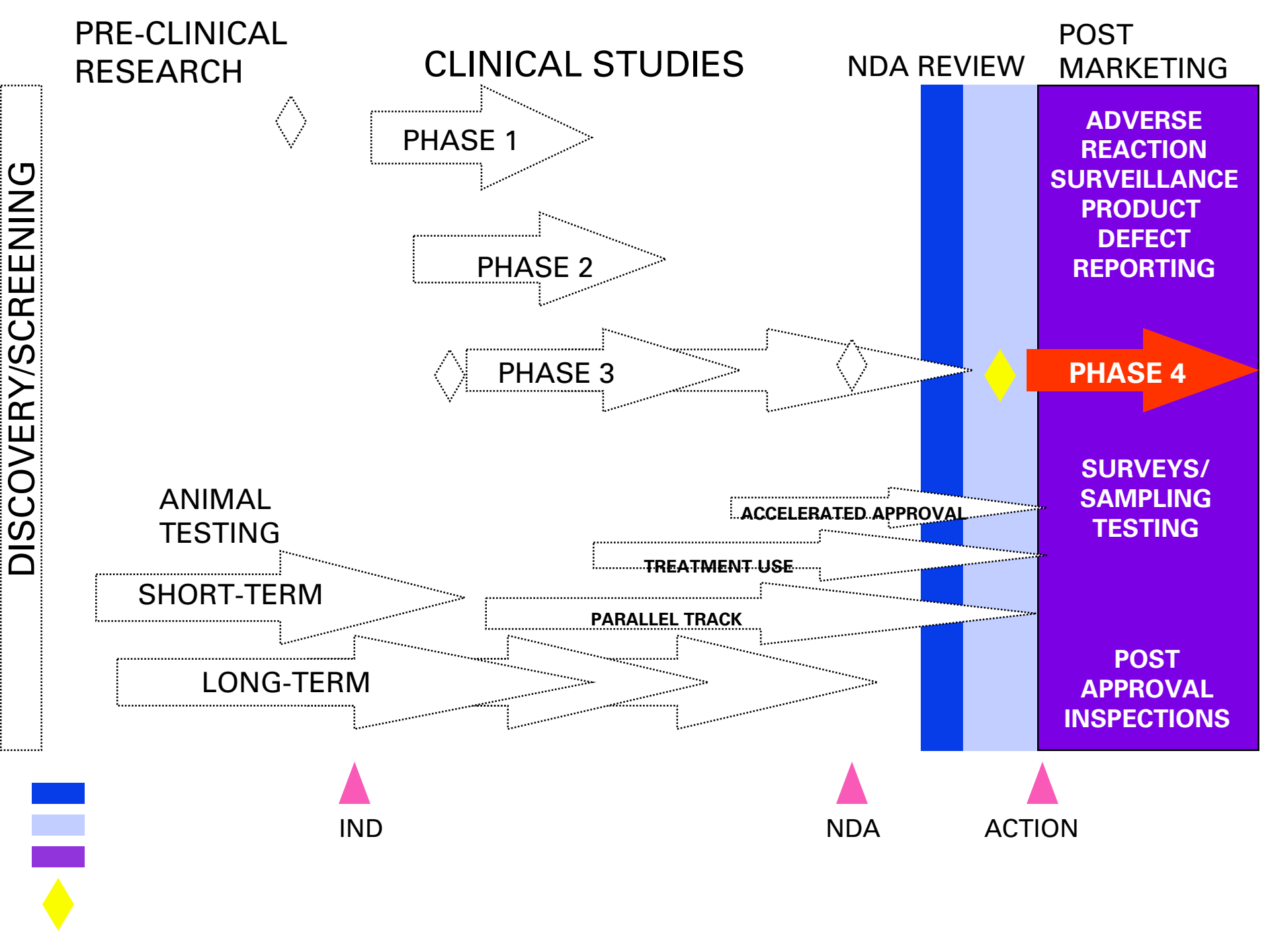
Main Findings:

Increased frequency of death in patients randomized to drugs realtive to placebo:

118/3353 (3.5%) vs. 40/1757 (2.3%)

OR = 1.54 (95% CI, 1.06 - 2.23, P=0.02)

Risk difference = 0.01 (95% CI, 0.004-0.02, P=0.01)

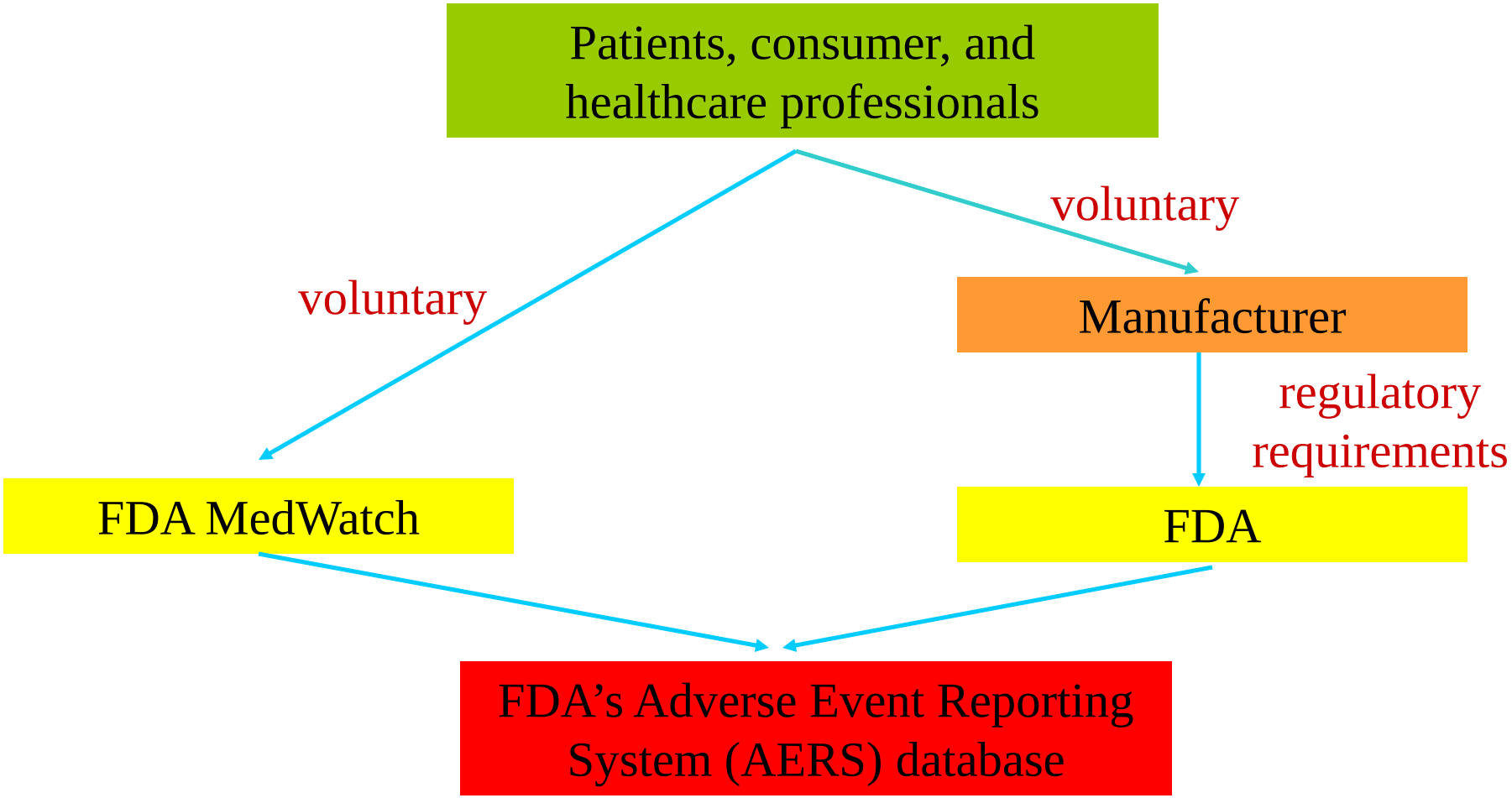

PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
POST MARKETING
DISCOVERY/SCREENING
PHASE 1
PHASE 2
PHASE 3
PHASE 4
ADVERSE REACTION SURVEILLANCE PRODUCT DEFECT REPORTING
SURVEYS/ SAMPLING TESTING
POST APPROVAL INSPECTIONS
ANIMAL TESTING
SHORT-TERM
LONG-TERM
ACCELERATED APPROVAL
TREATMENT USE
PARALLEL TRACK
IND
NDA
ACTION

Drug Safety Surveillance AFTER Marketing

- **Traditional methods:**
  - **“Spontaneous reporting” by health care professionals**
  - **Clinical trials**
  - **Population-based studies**
  - **Registries**

- **New opportunities via science and technology**

How post-marketing adverse event reports get to FDA



Post-marketing safety and the practitioner

www.fda.gov/medwatch

- Report adverse events to FDA
- Review new safety information
- Join e-list

MedWatch Voluntary Reporting Form FDA 3500 (top half)

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence #

A. PATIENT INFORMATION

1. **Patient Identifier**
In confidence

2. **Age at Time of Event, or Date of Birth:**

3. **Sex**
☐ Female
☐ Male

4. **Weight**
_____ lb
or _____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. **Date of Event** *(mm/dd/yyyy)*

4. **Date of this Report** *(mm/dd/yyyy)*

5. **Describe Event, Problem or Product Use Error**

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1
#2

2. **Dose or Amount** | **Frequency** | **Route**
#1
#2

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. **Diagnosis or Reason 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 #**
#1
#2

7. **Expiration Date**
#1
#2

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

Challenges in Analyzing Spontaneous Adverse Event Reports

- **The extent of reporting is not known, but is estimated to be less than 10% of adverse drug reactions**
- **Extent varies, may increase greatly after publicity**
- **The quality of reports is often suboptimal, and thus not always suitable for thorough medical evaluation**

Strengths and Limitations of Passive, Spontaneous Reports

- **Good for rare events that are generally the result of drug treatment, and do not have a high background rate**
- **Not good for events that are already common in the underlying populations**
- **Not good for events that occur long after drug exposure**

Identifying Signals in Spontaneous Reporting Databases is Challenging

- **Ideally, *rates* of adverse drug events could be calculated, but...**
  - **Numerators (exact number and extent of adverse events) impossible to know**
    - **Reporting by public not required**
  - **Denominators (drug exposure) impossible to know**
    - **Number of prescriptions filled is not an absolute measure of exposure due to non-compliance, misuse, abuse, etc.**

Example of a Rare by Serious Adverse Event: Felbamate and Aplastic Anemia

Twenty cases of patients with aplastic anemia developing while on felbamate

About 100,000 patients exposed to felbamate

Reporting rate in felbamate-exposed: 200/million

Incidence in general population: 2/million/year

Example of a case-control study:
Phenylpropanolamine (PPA) and hemorrhagic stroke

Cases:
Men and women ages 18-49 with subarachnoid or intracerebral hemorrhage, with no prior history of brain lesions and no history of stroke

Controls:
Two controls per case, selected by random digit dialing, matched on telephone exchange, sex, race, and age

Exposure:
Structured interview of cases and controls, to determine demographic, clinical, behavioral, and pharmaceutical information.
Medication information verified by subjects' identifying medications in a book of photographs of packages.
Exposure time-linked to onset of cases' symptoms (focal time) - first use within 24 hours prior to event; use within 3 days prior to event .

Source: Kernan et al. NEJM 2000;343:1826-1832

Example of a cohort study:

Phenylpropanolamine (PPA) and hemorrhagic stroke

Analysis:

Odds ratios, and 95% CIs, calculated using conditional logistic regression for matched sets, adjusted race (because of incomplete matching on this factor), history of hypertension, and current smoking status.

Results

Association Between the Use of Products Containing Phenylpropanolamine and the Risk of Hemorrhagic Stroke

	All Subjects		Women		Men	
Variable	Adjusted Matched Odds Ratio (95% CI)	P Value	Adjusted Matched Odds Ratio (95% CI)	P Value	Adjusted Matched Odds Ratio (95% CI)	P Value
Any use of products containing phenylpropanolamine	1.49 (0.84 – 2.64)	0.17	1.98 (1.00 – 3.90)	0.05	0.62 (0.20 – 1.91)	0.41
Cough or cold remedy	1.23 (0.68 – 2.24)	0.49	1.54 (0.76 – 3.14)	0.23	0.62 (0.20 – 1.92)	0.41
Appetite suppressant	15.92 (1.38 – 184.13)	0.03	16.58 (1.51 – 182.21)	0.02	--- (No events)	
First use of products containing phenylpropanolamine	3.14 (0.96 – 10.28)	0.06	3.13 (0.86 – 11.46)	0.08	2.95 (0.15 – 59.59)	0.48

Adapted from Kernan et al., NEJM 2000;343:1826-1832

Source: Kernan et al. NEJM 2000;343:1826-1832

Example of a cohort study: Statins and hospitalized rhabdomyolysis

Cohort:
Drug-specific inception cohorts of statin and fibrate users, based on data from 11 US health plans using automated claims covering prescription drugs, outpatient care, hospitalizations, and medical procedures

Exposure:
Algorithm developed to calculate person-time on drug for each patient based on prescription claims. Separate classifications for monotherapy and statin-fibrate combination therapy

Outcome:
Medical record review of all patients based on hospitalization claims with at least one ICD-9-CM code suggestive of severe muscle injury, followed by a blinded review to determine cases of rhabdomyolysis.

Source: Graham D et al. JAMA 2004;292:25885-2590

Example of a cohort study: Statins and hospitalized rhabdomyolysis

Analysis:

Relative risk estimates of rhabdomyolysis, adjusted for age, sex, and diabetes mellitus were calculated using Poisson regression. Incidence rates per 10,000 person-years of treatment, with 95% CIs, were calculated.

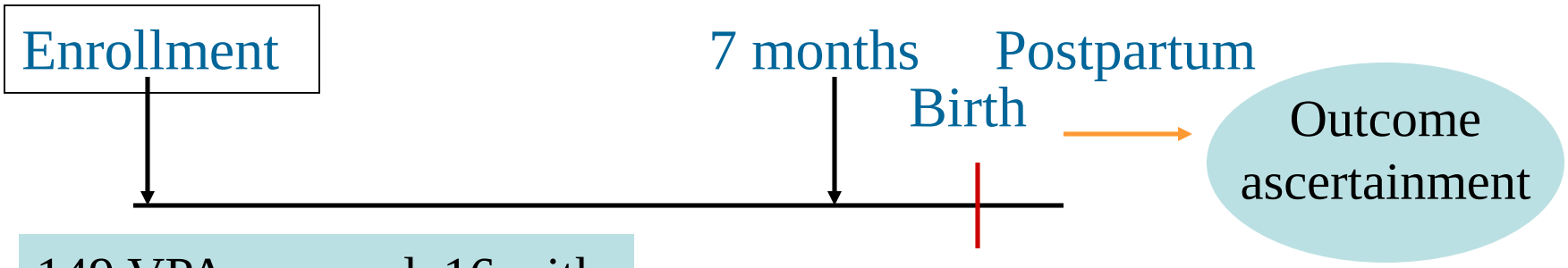
Results:

Rhabdoymyolysis per 10,000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug

		Combination Therapy	
Drug	Monotherapy Incidence Rates (95% CI)	Combination	Incidence Rates (95% CI)
Atorvastatin	0.54 (0.22-1.12)	Atorvastatin + fenofibrate	22.45 (0.57-125)
Cerivastatin	5.34 (1.46-13.68)	Cerivastatin + gemfibrozil	1035 (369-2117)
Pravastatin	0 (0-1.11)	No cases	0 (0-67.71)
Simvastatin	0.49 (0.06-1.76)	Simvastin + gemfibrozil	18.73 (0.47-104)
Fenofibrate	0 (0-14.58)	Fenofibrate + atorvastatin	16.86 (0.43-93.60)
Gemfibrozil	3.70 (0.76-10.82)	Gemfibrozil + cerivastatin	789 (166-2138)

Use of a Postmarketing Registry: Antiepileptic Drugs and Teratogenicity

Pregnant women with epilepsy on valproic acid



149 VPA-exposed, 16 with major malformations (10.7%, 95% CI: 6.3-16.9)

Internal comparator rate: 2.9% (95% CI: 2.0-4.1)

External comparator rate: 1.62%

Source: Wyszynski DF et al. Neurology 2005;64:961-965

Aftermath of Vioxx and other Drug Safety Problems: FDA Amendments Act of 2007

- **FDAAA laid out new authorities and drug safety programs for FDA**
- **FDAAA called for establishment of “active surveillance” system using health care databases**
- **Agency received additional resources to perform this work**

New FDA Authorities: FDAAA Title IX

- **Went into effect March 25, 2008**
- **FDA may require Risk Evaluation and Mitigation Strategies or REMS**
- **FDA may order postmarket studies and clinical trials**
- **FDA may order safety label changes**

Required Safety Label Changes

- **FDA has used this authority four times**

- **Each time for a class of drugs**
  - **Conventional antipsychotics: risk of higher mortality in elderly patients with dementia-related psychosis**
  - **Fluoroquinolones: increased risk of tendonitis/tendon rupture**
  - **ESA's: Conditions for use in cancer; dosing**
  - **TNF inhibitors: Add histoplasmosis warnings to existing boxed warning and Medication Guide**

New Scientific Approach to Drug Safety: The Sentinel Initiative

- **A National Strategy for Monitoring Medical Product Safety**
  - **Active surveillance to link electronic data that can be queried and analyzed**
  - **Augment current postmarketing surveillance tools**
- **The proposed model**
  - **Distributed Data System (data sources at remote locations; maintained by owners)**
  - **Increasingly may attempt to link data sources**
  - **Implemented through Public-Private Partnerships**
- **A National Forum to address issues related to the creation of such a system**

Why Now?

- **Technology now available**
- **FDA AA sets mandate**
  - **25 million people by 2010**
  - **100 million by 2012**
- **FDA-healthcare partnership acknowledges joint responsibilities for drug safety**
- **Foundation for FDA now available**

Ongoing Active Surveillance Pilot Projects

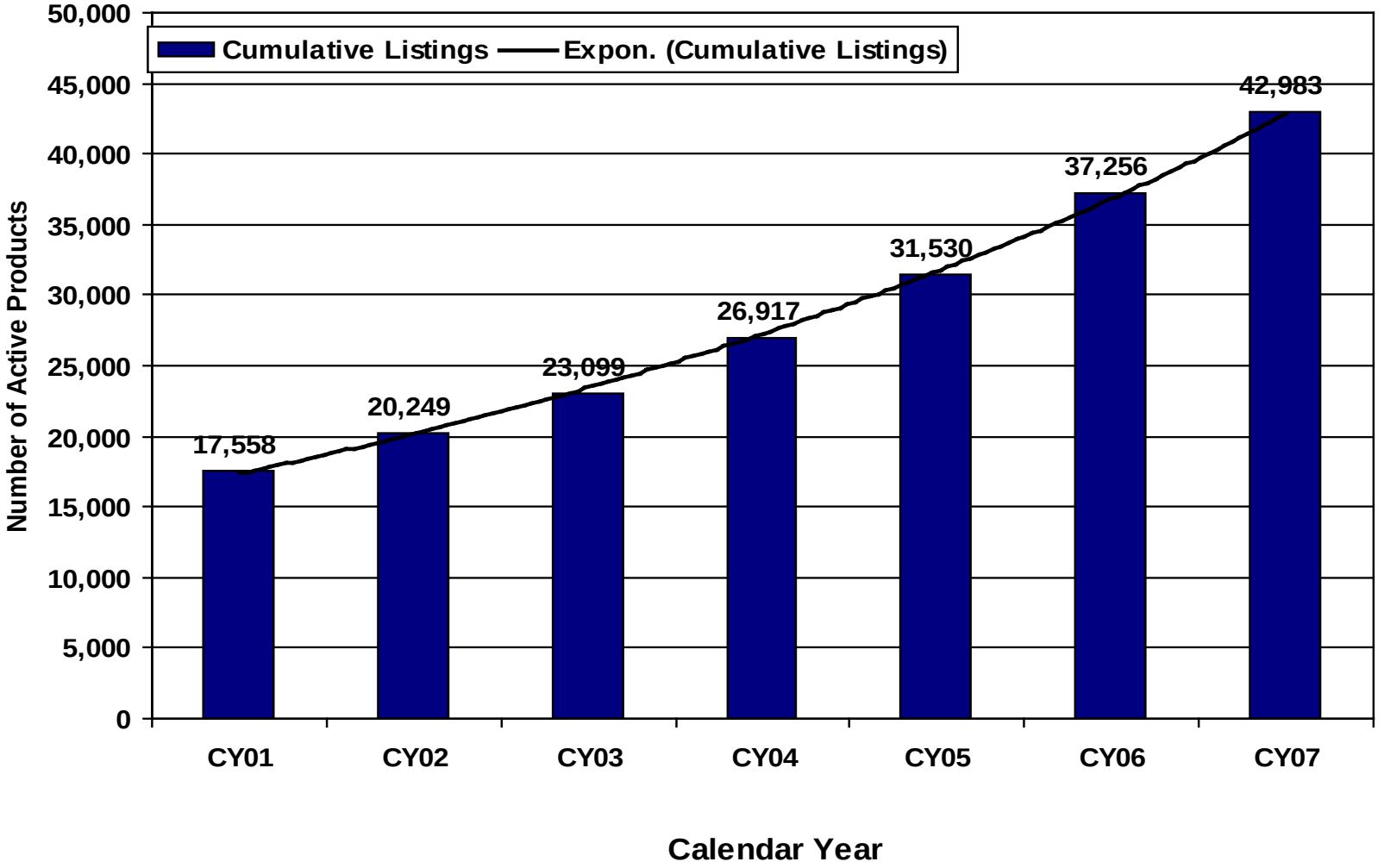
- **OMOP (Observational Medical Outcomes Pilot): FNIH, FDA, PhRMA, large methodologic evaluation pilot**
- **FDA-CMS**
  - **Part D and other Medicare data**
  - **Evaluate ability to find signals**
- **eHealth Initiative Pilot: "Connecting Communities for Drug Safety Collaboration**
  - **Methodologic pilot**
  - **FDA serving in advisory role**

Drug Quality: The *Sine qua non* of Drug Safety

- **If drugs are of poor quality, neither safety nor effectiveness can be relied upon**
- **In the US, people take high drug quality for granted**
- **In many parts of the world, this is not the case**
- **African regulators—attempted assassinations for combating drug counterfeits**
- **Globalization of drug manufacturing has brought this problem closer to home**

Number of Drug Products* Manufactured at Foreign Sites Has More Than Doubled Since 2001

Listed by Registered Manufacturing Sites

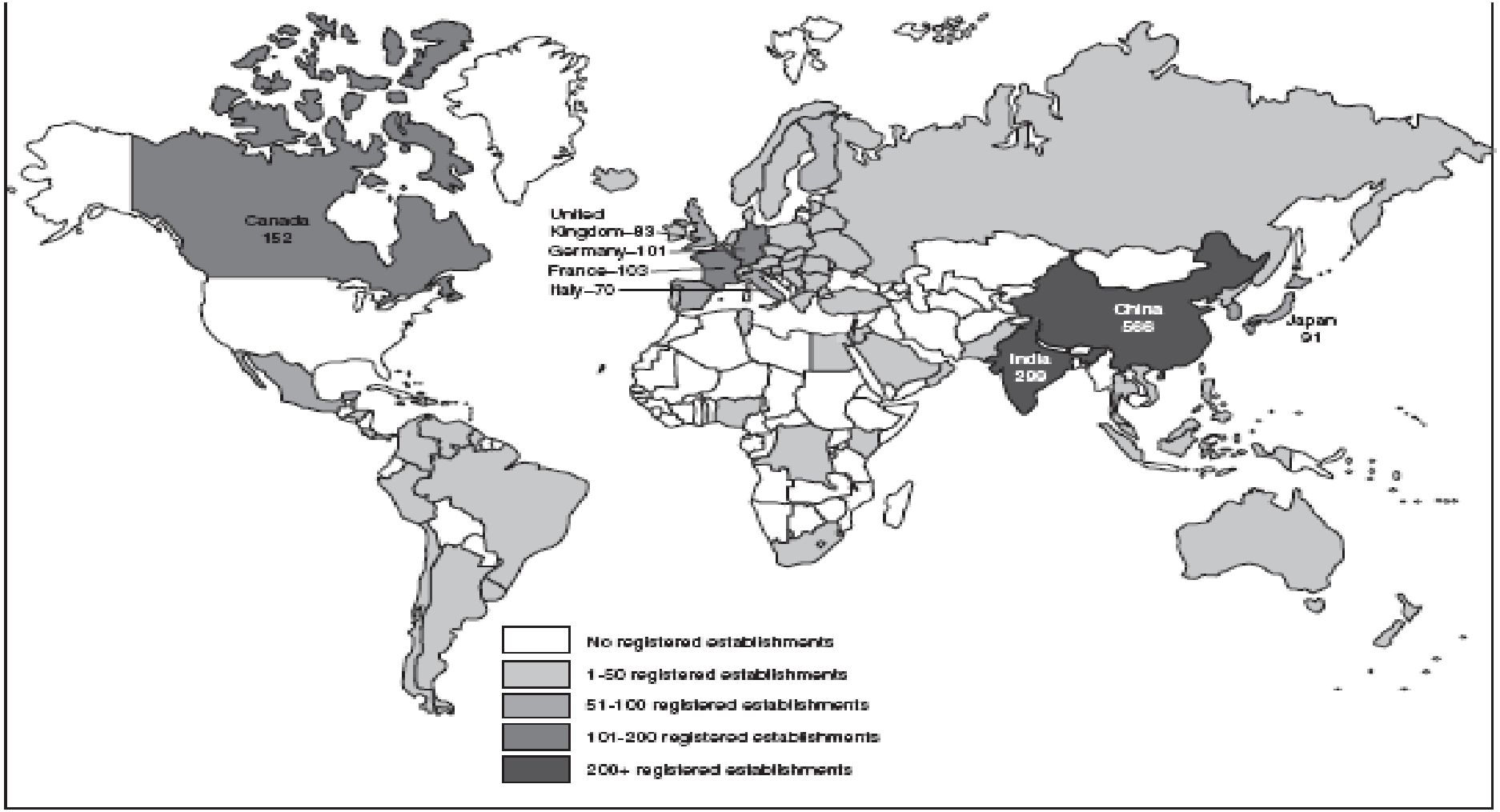


Data Source: FDA/CDER Drug Registration and Listing System

* Finished drugs, intermediates and APIs; Products active on 3/18/2007

Mission v. Challenges

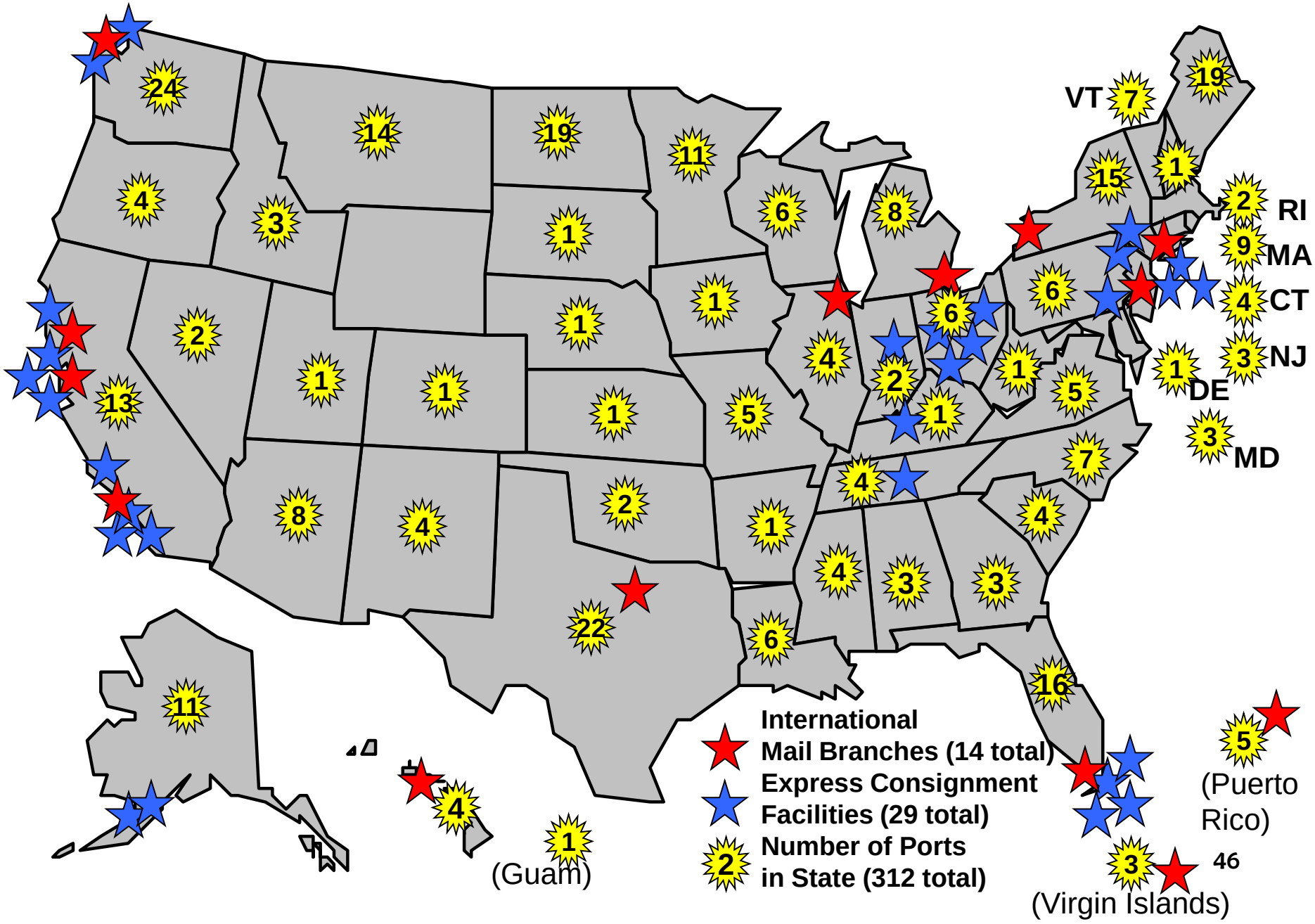
Manufacturing of Many FDA-Regulated Drug Products Has Moved Overseas



Source: GAO analysis of FDA data.

Note: These counts include foreign establishments that manufactured human drugs, biologics, and veterinary drugs; FDA was unable to provide the number of registered establishments specifically manufacturing human drugs.

For Drug Imports, Many Possible “Points of Entry”



Diethylene Glycol

- **Medications contaminated with DEG in various countries**
  - **2007 – DEG contamination in toothpaste**
  - **2006 – Panama – 115 deaths**
  - **1998 – India – 33 deaths in children**
  - **1996 – Haiti – 85 deaths in children**
  - **1990 – Bangladesh – over 300 children with kidney failure**

DEG in Cold Medicine

Ángel Franco/The New York Times (http://www.nytimes.com/2008/02/14/world/americas/14panama.html?_r=2&oref=slogin&oref=slogin)

In 2006, cold medicine containing DEG in Panama poisoned at least 174, 115 of them fatally. Drug ingredient containing DEG was linked to an unlicensed Chinese chemical plant.

Heparin

U.S. Identifies Tainted Heparin in 11 Countries - New York Times - Microsoft Internet Explorer

File Edit View Favorites Tools Help

The New York Times
nytimes.com

PRINTER-FRIENDLY FORMAT SPONSORED BY UNDER THE SAME MOON

April 22, 2008

U.S. Identifies Tainted Heparin in 11 Countries

By GARDINER HARRIS

WASHINGTON — A contaminated blood thinner from China has been found in drug supplies in 11 countries, and federal officials said Monday they had discovered a clear link between the contaminant and severe reactions now associated with 81 deaths in the United States.

But a Chinese official disputed the assertion that the contaminant found in the drug, heparin, caused any deaths and insisted that his country's inspectors be allowed to inspect the American plant where the finished heparin vials were made. He said any future agreement to allow American inspections of Chinese firms should be reciprocal.

"We don't have a strong evidence to show that it is heparin or its contaminant that caused the problem," said the official, Ning Chen, second secretary at the Chinese Embassy.

Mr. Chen said that illnesses associated with contaminated heparin had occurred only in the United States, which he said suggested that the problem arose in this country.

Dr. Janet Woodcock, director of the Food and Drug Administration's drug center, said that German regulators uncovered a cluster of illnesses among dialysis patients who took contaminated heparin. She said Chinese officials had conceded that heparin produced in their country contained a contaminant, though they say it was not connected to the illnesses.

"Heparin should not be contaminated, regardless of whether or not that contamination caused acute adverse events," Dr. Woodcock said. "We are fairly confident based on the biological information that we have had that this contaminant is capable of triggering these adverse reactions."

Done Internet

start Calen... Interv... U.S. I... Micros... 12:28

Where a Drug Begins - WSJ.com - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://online.wsj.com/article/SB120352438415380201.html?slide=3 Go Links

3/16

More Slideshows

Email Print Link

Where a Drug Begins

More than half the world's heparin, the main ingredient in a widely used anti-clotting medicine, gets its start in China's poorly regulated supply chain. (See related article.)

The process for getting raw heparin is rather simple. First, the company picks up barrels of pig intestines from slaughterhouses.

Gordon Fairclough

Where a Drug Begins - WSJ.com - Microsoft Internet Explorer

Edit View Favorites Tools Help

Back Search Favorites

dress http://online.wsj.com/article/SB120352438415380201.html?slide=3 Go Links

2/16

More Slideshows

Email Print Link

Where a Drug Begins

More than half the world's heparin, the main ingredient in a widely used anti-clotting medicine, gets its start in China's poorly regulated supply chain. (See related article.)

The men wring pulp from pig intestines and heat it in open cement vats.
After further processing by more sophisticated plants, the chemical is made into intravenous drugs given to patients around the world having surgery or patients who need kidney dialysis or blood transfusions.

Gordon Fairclough

Done Internet

Where a Drug Begins

More than half the world's heparin, the main ingredient in a widely used anti-clotting medicine, gets its start in China's poorly regulated supply chain. (See related article.)

After it is dried, the crude heparin (left), goes through many steps aimed at ridding it of harmful substances before it ends up in medications.
The lack of consistent oversight of China's heparin industry highlights the regulatory gaps as pharmaceutical companies become increasingly global in their purchase of ingredients.

Gordon Fairclough

Science Solved Heparin Mystery

- **FDA laboratories identified aberrant signal on NMR testing**
- **Work with academic collaborators on several continents rapidly identified over-sulfated chondroitin sulfate: not a naturally occurring compound**
- **Animal and in vitro testing revealed adverse biological activity**
- **Results rapidly published**

Heparin Timeline
April

April 23, 2008
Guerrini M et al. Oversulfated chondroitin is a contaminant in heparin associated with adverse clinical events.
http://www.nature.com/naturebiotechnology

April 23, 2008
Kishimoto TK et al. Contaminated heparin associated with adverse clinical events and activation of the contact system.
http://www.nejm.org

Drug Safety is an Ongoing Challenge

- **New scientific approaches will improve our understanding of drug safety during drug development**
- **New surveillance techniques will help us learn more, faster, about safety of drugs after they are approved**
- **New science such as pharmacogenomics will provide additional tools for clinicians to minimize patient risk**
- **Risks from drugs quality problems are on the rise: FDA must increase its vigilance**