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Pharmacovigilance and Drug Safety: Assessing Future Regulatory and Compliance Developments

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Assessing Future Developments

- Pharmacovigilance - A definition
- Four drivers of change
- Premarket pharmacovigilance - Shifts in FDA guidance
- Postmarket pharmacovigilance - FDAAA and the FDA Sentinel Initiative
- The emerging science of safety - What we don’t know and will need to figure out.

A Definition of Pharmacovigilance –

World Health Organization (WHO):

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

FDA Guidance for Industry.
ICH. E2E Pharmacovigilance Planning.
April 2005.

A Framework of Pharmacovigilance –

Entire product life-cycle

- Global
- Science-based approach to risk documentation and evaluation
- Collaboration between regulators, industry, and other stakeholders
- “The world is flat” – Instant global news

The Questions of Pharmacovigilance –

- Important identified risks: What is known?
- Important potential risks: What safety signals must be confirmed or rebutted?
- Important missing information: What are limitations of the safety database?
  - Extent of drug exposure
  - Patients excluded from premarket studies
  - Changes in real world use in practice of medicine

A physician's perspective –

- How do we improve the detection of safety signals?
- How do we make the decision that a new safety signal is likely to be "real" and actionable?
- How and when do we communicate to patients and physicians to enhance medical decision making?

The Drivers – Changing Expectations

- FDA and ICH: International Conference on Harmonisation
  - United States, European Union, Japan
- Institute of Medicine Drug Safety Report, 2006
- OIG Report, Sept. 2007. “The Food and Drug Administration’s Oversight of Clinical Trials”
- FDA Amendments Act of 2007. Title IX.
  - FDA Sentinel Initiative, May 2008

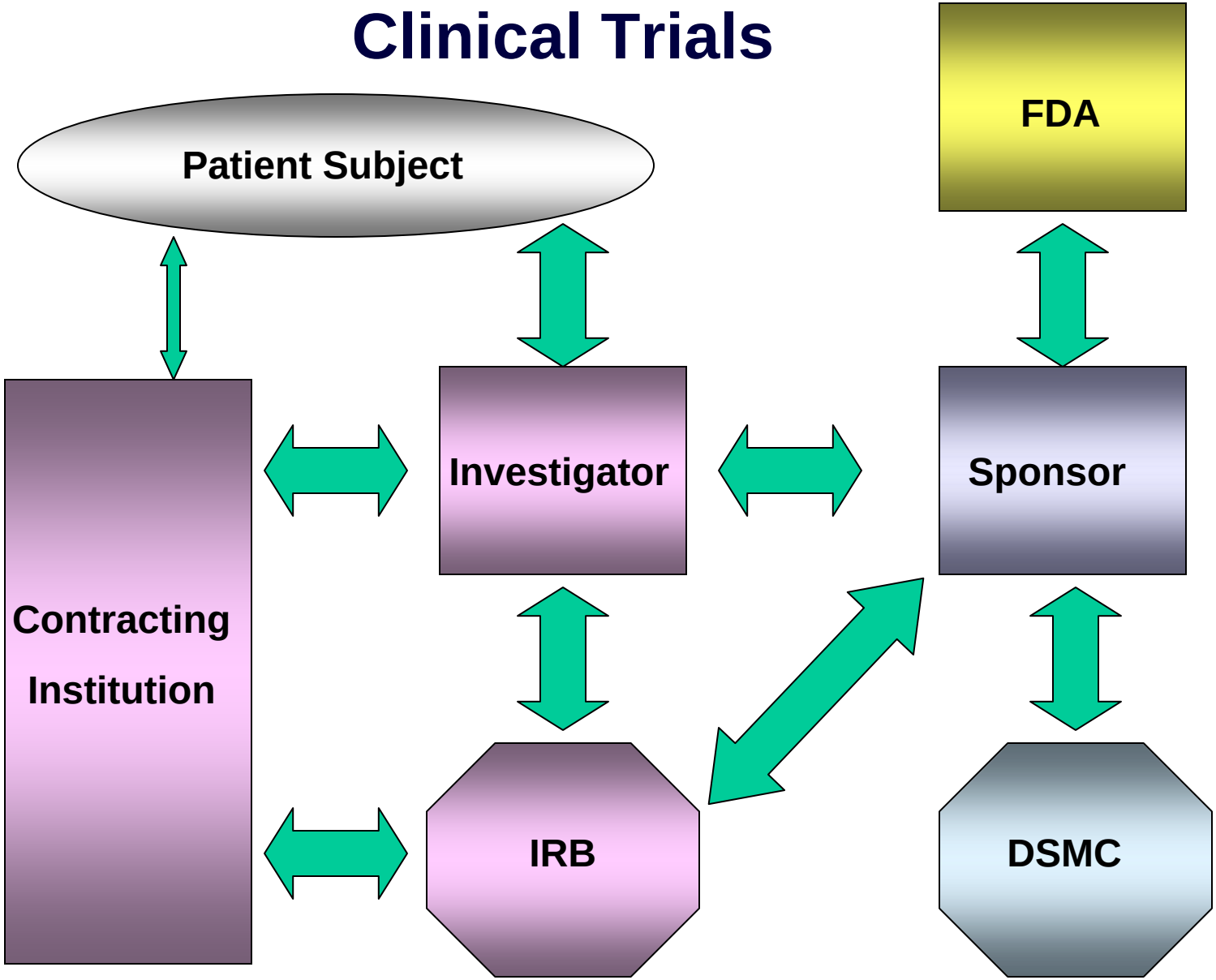
OIG Clinical Trials Report Sept 2007

- Inadequate on-site attention to safety compared with data integrity
  - FDA (Bioresearch Monitoring, BiMo)
  - IRBs
  - And, by extension, Sponsors and Investigators
- Excess reliance on voluntary compliance, incomplete data, insufficient action
- Need for expanded FDA safety oversight beyond the Investigator

Pharmacovigilance during Clinical Trials

- Sponsor oversight of Investigator compliance
- Analysis of incidence of adverse events
  - Data (Safety) Monitoring Committees (DSMC)
- Larger trials and longer duration of collection of safety data compared with efficacy data
  - Condition of approval safety surveillance studies
- DSUR: Expanded global regulatory and IRB disclosure

Safety Communication in FDA-regulated Clinical Trials



Pharmacovigilance in Clinical Trials: Whose Job is It?

- **Reporting of serious adverse effects**
  - Predominantly **Sponsor** and **Investigator** responsibilities
- **IRB responsibilities**
  - Protection of the safety and welfare of human subjects
  - Extreme dependence on interim safety data provided by investigators and Sponsors
- **Data (Safety) Monitoring Committee**
  - Increasingly important and central role in clinical trial conduct
  - Approximately 740 FDA-regulated trials with DSMC
  - Careful definition by charter of responsibilities and process for communication to Sponsor is critical

Adverse Events - Reporting in IND Studies

– Reporting under FDA IND regulations

- **Definitions**: "any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug" (21 CFR § 312.64(b)), AND

  "all ***unanticipated problems*** involving risks to human subjects or others" (21 CFR § 312.53(c)(1)(vii), § 312.66, § 56.108(b)(1))
- **Investigator**: Report AEs promptly to Sponsor, and if "alarming," immediate reporting, AND report all *unanticipated problems* to IRB
- **Sponsor**: Notify all investigators of "any adverse experience associated with the use of the drug that is both ***serious and unexpected***" 21 CFR § 312.32(c)(1)(i)(A)(B), AND *analyze the significance of the current adverse experience in the light of previous reports* (§ 312.32(c)(1)(ii))

Pharmacovigilance in Clinical Trials: FDA Policy is Evolving

- FDA Guidance for Clinical Investigators, Sponsors, and IRBs. *Adverse Event Reporting - Improving Human Subject Protection*. *Draft.* April 2007.
  - Clarification of "prompt reporting to IRB of all *unanticipated problems*"
- FDA Guidance for Industry. *Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators*. *Draft.* May 2007.
- FDA Guidance for Sponsors. *Establishment and Operation of Clinical Trial Data Monitoring Committees. Final.* March 2006.

Adverse Events: Focus on Incidence

- "For events that are part of the underlying disease process or that occur at reasonably large background rates in the subject population, individual reports are almost never informative. Before such events can be determined to be "unanticipated" and the significance of the events can be assessed, a comparison of the incidence of the event in treated and untreated patients is needed."
  - FDA Guidance for Industry. Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators. Draft. May 2007.
- Case example: CV events in trials of diabetes drugs

Adverse Event Reporting during Clinical Trials: FDA Policy is Evolving

Anticipate a greater emphasis on:

- Context

  How do adverse events relate to a larger experience of similar events and trends?

- Incidence, including DSMC oversight

  Analysis of event rate and future probability, especially a signal of an increase in rate when the event is common and expected in the population

- Access

  Including safety data of Investigator-Sponsored studies

Pharmacovigilance: Preplanning Detection in Clinical Trials

- "Demonstration of adequate safety necessitates a larger sample size than demonstration of efficacy…"
- Preplanning and justification of sample size to detect AEs
  - e.g., statistical power to rule out with 95% confidence a specific percent increase in incidence of adverse events that are expected to occur at a given rate in control group
- Preplanning for inclusion of significant clinical comorbidities (e.g., diabetes, dyslipidemia, hypertension)
- Preventing missing safety data from premature dropouts
  - FDA Guidance for Industry. Developing Products for Weight Management. Draft. May 2007.

Pharmacovigilance: Harmonizing Global Development Safety Update Reports

- Draft ICH harmonized guidance released June 5, 2008
  - "Developmental Safety Update Report E2F"
- Intended to incorporate all current regulatory components and replace existing annual US IND report and EU annual report. Also Japan.
- More comprehensive annual safety reporting
  - Increased assurance of protection for trial subjects
  - *New* Summary of Important Risks – highlights issues for industry and regulators to monitor
  - *New* Advice rendered by regulators that modifies development
  - *New* Executive Summary for stakeholders, including IRB.

FDA Amendments Act of 2007

Pub. L. No. 110-85 § 905 requires FDA to

- Access new public and private data sources
- Develop a system to "link and analyze product safety data" from these sources
- Develop tools to detect and evaluate safety signals
- Establish an active "postmarket risk identification and analysis" program including
  - 25 million patients by 2010 and 100 million patients by 2012
- Disclose to the public

FDA Sentinel Initiative - May 22, 2008

"The Sentinel Initiative: National Strategy for Monitoring Medical Product Safety"

http://www.fda.gov/oc/initiatives/advance/sentinel/

- New electronic system, called the Sentinel System
- Targeted queries of electronic health records, patient registry data, insurance claims data, and other large healthcare information databases
- CMS final rule, effective June 27, 2008, allows sharing of prescription drugs claims data for Medicare Part D enrollees
  - 73 Fed. Reg. 30664 (May 28, 2008)

Sentinel – Mining Safety Signals

Powerful and vast electronic data sources

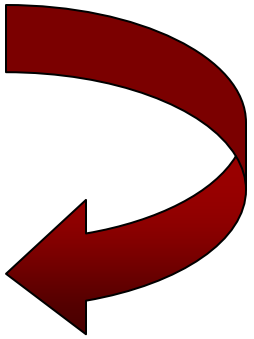
- CMS Part D claims database – 25 million Medicare Part D enrollees
- Veterans Administration, and other federal sources
- Kaiser Permanente – 6.6 million member database
  - FDA collaboration since 2005 identifying CV events related to use of Vioxx
- WellPoint, Inc. – 35 million member database
- UnitedHealth, with i3 Drug Safety

Sentinel – From Detection to Analysis

- **Passive Surveillance**
- **Stimulated Reporting**
  - New products or limited periods
  - Predesigned methods for detection and description
  - Problems: Selective reporting and incomplete data
  - Cannot generate accurate incidence rates
- **Active Surveillance**
  - Continuous preorganized process – specific populations, drug, and adverse events
- **Registries**
  - Useful for amplification of rare signal
  - Cannot prove association in absence of control group

Sentinel – From Detection to Analysis

- **Comparative Observational Studies**
  - **Cross-sectional Study (Survey)**
    - Crude possible association but cannot define temporal relationship between drug exposure and outcome
  - **Case-control Study**
    - Relative risk of event can be estimated.
  - **Cohort Study**
    - A population-at-risk for the disease (or event) is followed over time. Can calculate incidence rates.
- **Meta-analysis of multiple clinical trials**
- **Targeted clinical safety trial, often RCT**



Sentinel – From Analysis to Action

- FDA partnerships with public and private payers allow opportunity for unprecedented rapid action to remove access of specific patients to specific drugs
- Risk of action, including harm, by acting on "false positives" or delaying action on "false negatives"
- **Signal detection to validation is critical**:
  - Is the signal of risk "real"?
  - What level of uncertainty is acceptable?
  - Can potential, but uncertain, risk be mitigated while better scientific data is acquired?
  - An emerging science of safety – not the same as the science of clinical trials

Deciding Risk is "Real" in a Clinical Trial

Decision making is well-defined by regulatory practice and consensus-based clinical science standards

- Reliance on prospective randomized clinical trial as highest standard of proof
  - Bias of confounding variables is mitigated by randomization
  - Predefined questions are tested and events are adjudicated
  - Conducted in defined and monitored population
- Statistical standards – agreement about the level of confidence required to conclude that a result is not due to play of chance
- Not designed or powered for detection of late or very low-frequency safety events in real world use

Deciding Risk is "Real" in Postmarket Safety Surveillance

There is not yet regulatory or scientific consensus:

- Effective and reliable methods of safety signal validation using population databases
  - Correcting for bias when confounding factors are not mitigated by randomization
- Evidentiary standards required for decision making
  - Acceptable statistical standards of certainty that a safety signal is not the play of chance, or
  - Agreement on action when the degree of uncertainty is high
- Science of safety signal analysis is evolving and participation of all stakeholders is essential

Safety Signal Analysis and Communication

When to notify and act?

- If too early, the communication may be inaccurate, not useful to guide patient choice and therapy, or harmful
- If too late, potentially preventable injury or deaths may occur

Whom to notify?

- The physician and public. And, direct-to-patients?

What information? Too little? Too much?

- What should trigger a public safety advisory?
- Trend analysis is critical: Is a safety signal the play of chance or likely to be systemic and occur in future patients?

In Summary - The Future is Now

- Premarket clinical trial pharmacovigilance
  - More complex trial design, duration, and size
  - During the trial - AE incidence, comparison, and reporting
  - DSMC participation
  - Oversight of investigators
  - Expanded US and global safety reporting
- Postmarket pharmacovigilance
  - Access to multiple large population databases
  - Competency in query and analysis
  - Capability for risk mitigation of early signals
  - Streamlined decision making and communication

Thank you

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FDA and Clinical Investigation of Drugs

- **FDA requirements for clinical investigations of drugs and biologics include:**
  - Investigational New Drug Application (IND)
  - Institutional Review Board (IRB) review and approval of the protocol and informed consent procedure
  - Informed Consent (*a process, not just a signed form*)
  - Good Clinical Practice (GCP)
  - Bioresearch Monitoring ("BiMo")
- **Relevant regulations:**
  - 21 CFR § 312 (IND)
  - 21 CFR § 50 (Informed consent)
  - 21 CFR § 56 (IRB and parent institution)
  - 21 CFR § 54 (Financial disclosure of investigators)