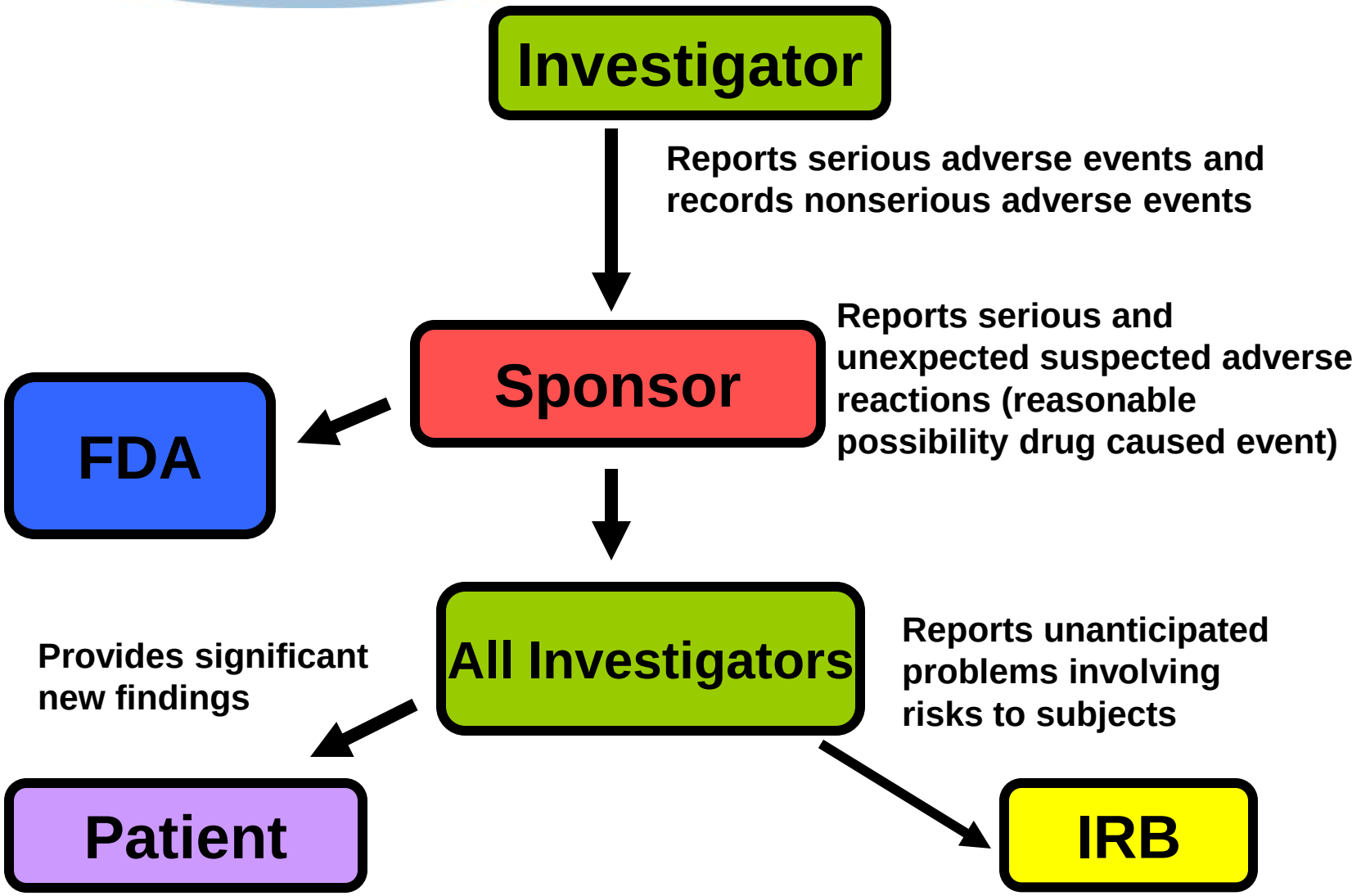
IND Safety Reporting Final Rule

CTTI Expert Meeting

October 4, 2010


Investigator
Reports serious adverse events and records nonserious adverse events
Sponsor
Reports serious and unexpected suspected adverse reactions (reasonable possibility drug caused event)
FDA
All Investigators
Provides significant new findings
Reports unanticipated problems involving risks to subjects
Patient
IRB

Overview

- The rule:
  - Codifies FDA's expectations for timely review, evaluation and submission of relevant and useful safety information
  - Implements internationally harmonized definitions and reporting standards
  - Clarifies confusing terminology in existing regulations
- Thus, improves the utility of premarket safety reports which enhances human subject protection

Background

- Safety Reporting Requirements Proposed Rule - published March 2003
  - Included premarket (312.32), postmarket (310.305, 314.80, 600.80), and blood and blood components (606.170)
  - Goals were to improve the quality of reports, expedite FDA's review of critical safety information, and harmonize with international standards
- Received 110 comments

FDA decided to split the proposed rule into two final rules: pre- and postmarket

New Definitions

- ***Adverse event*** – any untoward medical occurrence associated with the use of a drug in humans, *whether or not considered drug related*

- ***Suspected adverse reaction***
  - Any adverse event for which there is a *reasonable possibility* that the drug caused the adverse event
  - "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and adverse event

Expedited Reporting Requirement – Serious and Unexpected Suspected Adverse Reaction

- Any suspected adverse reaction that is both serious and unexpected
  - *Suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the event
  - *Unexpected* means not listed in the investigator brochure
  - *Serious* means results in death, is life-threatening, hospitalization, etc.
- Report only if there is evidence to suggest a causal relationship between the drug and the adverse event

Examples of Evidence

- Single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

- An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Other New Expedited Reporting Requirements

- Study endpoints must be reported per the protocol (not in an IND safety report) unless there is evidence suggesting a causal relationship with the drug

- Sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

- Other findings that suggest a significant human risk must be reported (e.g., epidemiologic data, animal studies)

Draft Guidance Topics

- Provides examples and rationale for new definitions and requirements
- Discusses a systematic approach for safety surveillance
- Provides advice on other safety reporting issues that have generated questions from sponsors and investigators (e.g., Investigator brochure, unblinding)

Looking Forward

- Implementation:
  - Effective March 28, 2011
- Expected outcome:
  - Investigators (and FDA) should receive fewer individual reports, but reports should be more complete and meaningful
- To achieve this:
  - Protocols may need to be more specific
  - Sponsor will have more responsibility for aggregation and analysis of adverse events