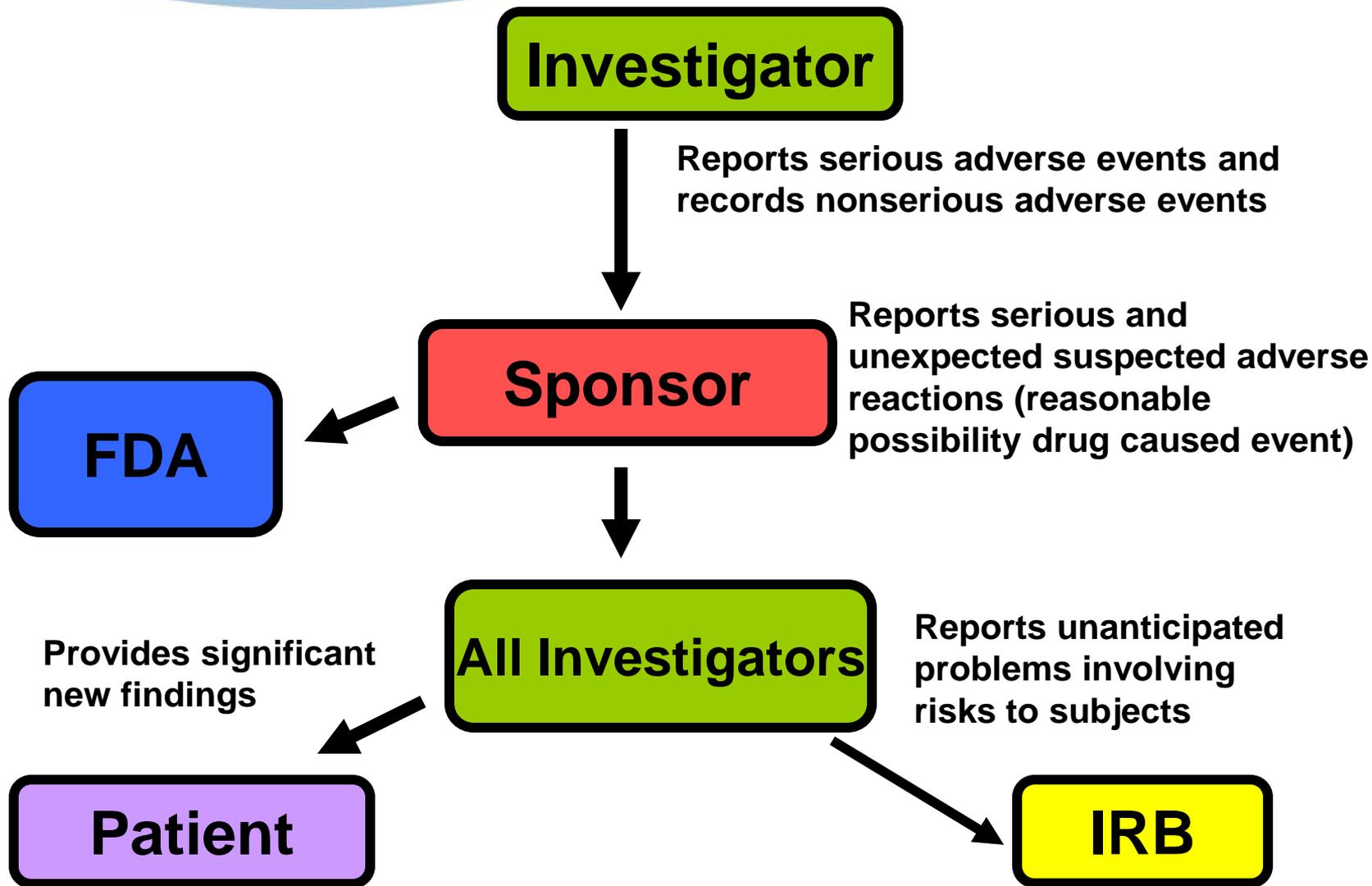




IND Safety Reporting Final Rule

**CTTI Expert Meeting
October 4, 2010**



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