NEW Draft Guidance:

# Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies

Overview of FDA Draft Guidance
Issued for Comment

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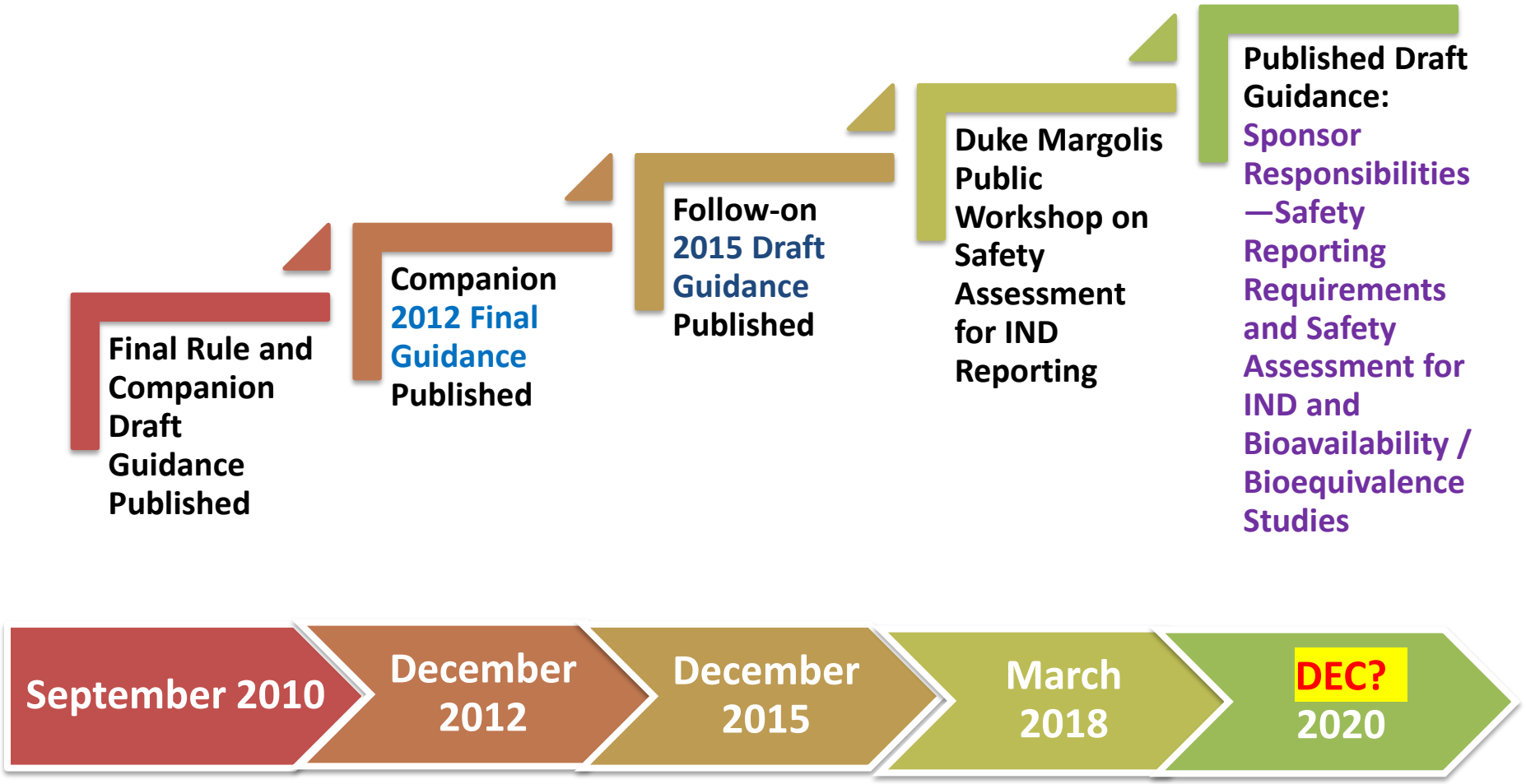
# Outline

- **Background**
  - **History and overview of 2010 IND Safety Rule and Related Safety Reporting Guidance**
- **NEW Draft Guidance—Overview of new content:**
  - **Reporting & Aggregate Analyses: Considerations & Methods**
  - **Pooling Data Across Studies**
  - **Aggregate Analyses: Reporting Thresholds**
  - **Entity(ies) Who Should Review Safety Information**
  - **Unblinding of Safety Data and Implications**
  - **Safety Surveillance Plan**
  - **IND Safety Reporting for Marketed Drugs and Active Control**
  - **Electronic reporting using ICH E2B standards**
  - **New flowcharts for IND safety reporting**

# Guidance: Timeline of IND Safety Reporting Policy Development



# Background:
# 2010 Final Safety Reporting Rule

- Published, Sept. 29, 2010. Effective, March 28, 2011
- Amended IND safety reporting requirements under 21 CFR part 312 and added safety reporting requirements for BA / BE studies not conducted under IND under 21 CFR part 320
- Goal of 2010 Final Rule: Improve the utility and quality of premarket expedited safety reports, thereby enhancing human subject protections by:
  - Eliminating confusing terminology
  - Clarifying sponsor and investigator responsibilities
  - Eliminating uninformative individual case reports

# IND Safety Reporting Final Rule (21 CFR Part 312.32)

- Provided definitions used for safety reporting to make clear when to submit expedited safety reports
- Introduced "suspected adverse reaction," to replace "associated with the use of the drug"
  - adverse event for which there is a reasonable possibility that the drug caused the adverse event
- Defined "reasonable possibility" to mean that that there is evidence to *suggest a causal relationship* between the drug and adverse event (AE)
  - Changed from the proposed definition of "relationship cannot be ruled out"
- Directed the reporting toward more interpretable findings and decreased submission of uninformative safety reports, e.g., reports of events that were manifestations of the underlying disease, serious events common in the study population, or study endpoints.

# IND Safety Guidance Development:
# 2012 Final Guidance

- **2012 final guidance *Safety Reporting Requirements for INDs and BA/BE Studies*, *intended to help implement the 2010 regulation changes,* provides recommendations on:**
  - **Evaluating safety information, including periodic review and analysis of entire safety database to identify safety signals**
  - **When and how to submit a safety report**
  - **Unblinding and other safety reporting issues**

# IND Safety Guidance Development:
# 2015 Draft Guidance

- **Follow-on 2015 draft guidance *Safety Assessment for IND Safety Reporting* was developed to facilitate evaluation of events requiring aggregate analyses**
- **The 2015 draft guidance provided recommendations on:**
  - **Planned unblinding of safety data to assess for aggregate safety signals**
  - **Composition and role of a safety assessment committee (SAC), generally thought to be necessary for aggregate analyses**
  - **Aggregate analyses for comparison of adverse event (AE) rates across treatment groups**
    - **Pooling data across studies**
    - **Reporting thresholds for IND safety reporting**
  - **Development of a safety surveillance plan and recommendation to submit to the IND**

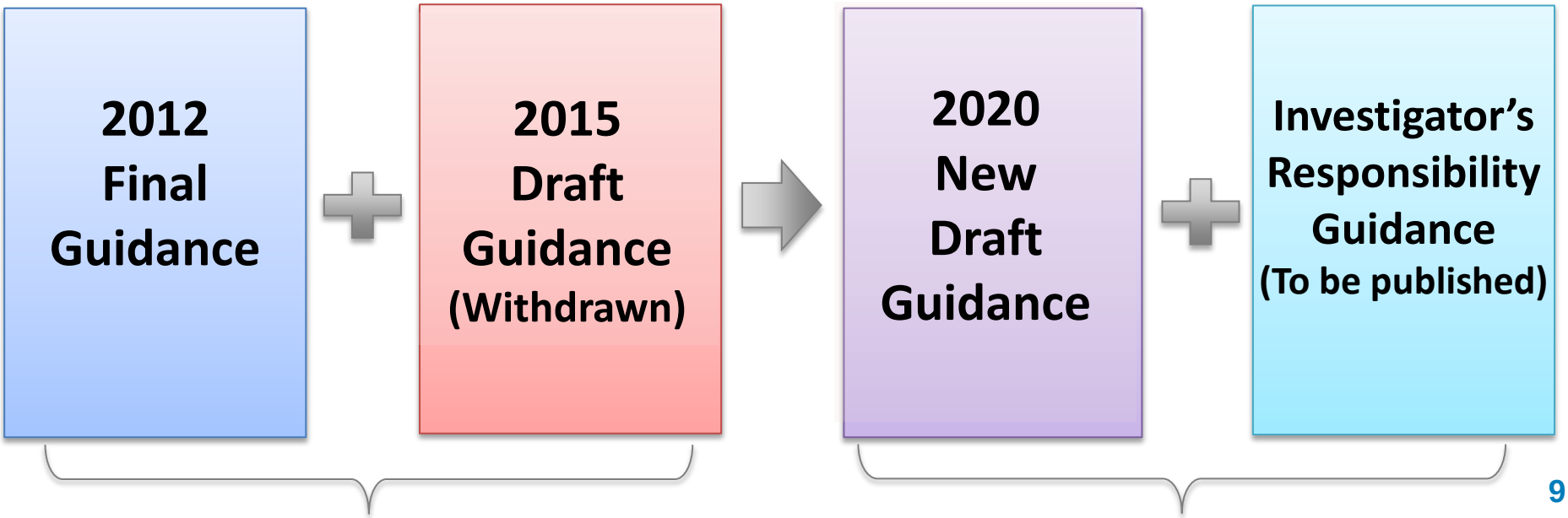
# What We Have Heard: Challenges with Implementation of 2015 Draft Guidance

| | |
|---|---|
| **Trial integrity** | **Risks of disclosure, and consequent trial impact, with repeated unblinding; impact of unblinded (or blinded) safety reports to sites** |
| **Trial complexity/ overlapping responsibilities** | **Adding new infrastructure, integration of new committee (SAC) with DMC, and internal company safety monitoring group** |
| **Separating signal from noise** | **Difficulties with *pooling* across a program; *multiplicity issues* with comparison across multiple event types and with multiple looks – sorting out false from true positives – when and what to report, risks to trial of "over-reporting"** |
| **Need for SAC** | **DMC may be able to carry out objectives of SAC, review of imbalances and flag potentially meaningful signals for reporting** |

# 2020 New Draft Guidance:

## *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*

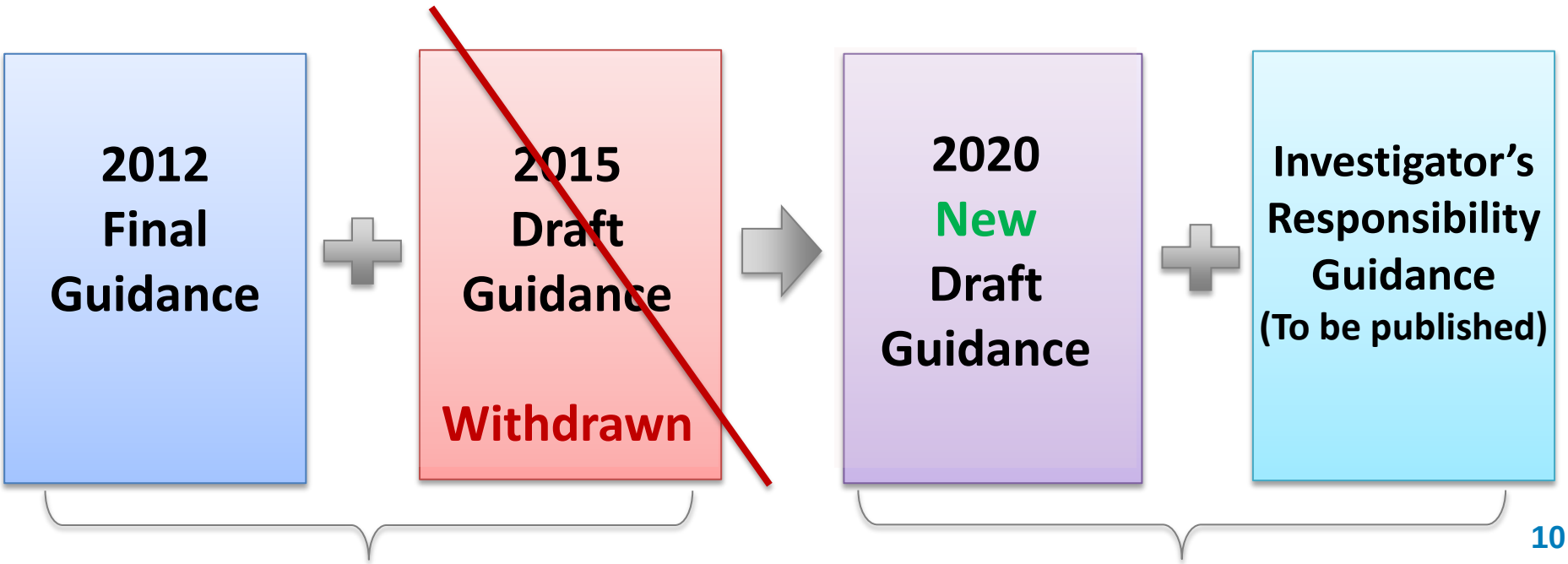
- **This 2020 Guidance is a comprehensive draft that**
  - **combines 2012 and 2015 guidances ⟹ 2015 guidance withdrawn**
  - **removes section regarding Investigator Responsibilities for IND and BA/BE safety reporting ⟹ Investigator's Responsibilities guidance to be published as separate guidance**



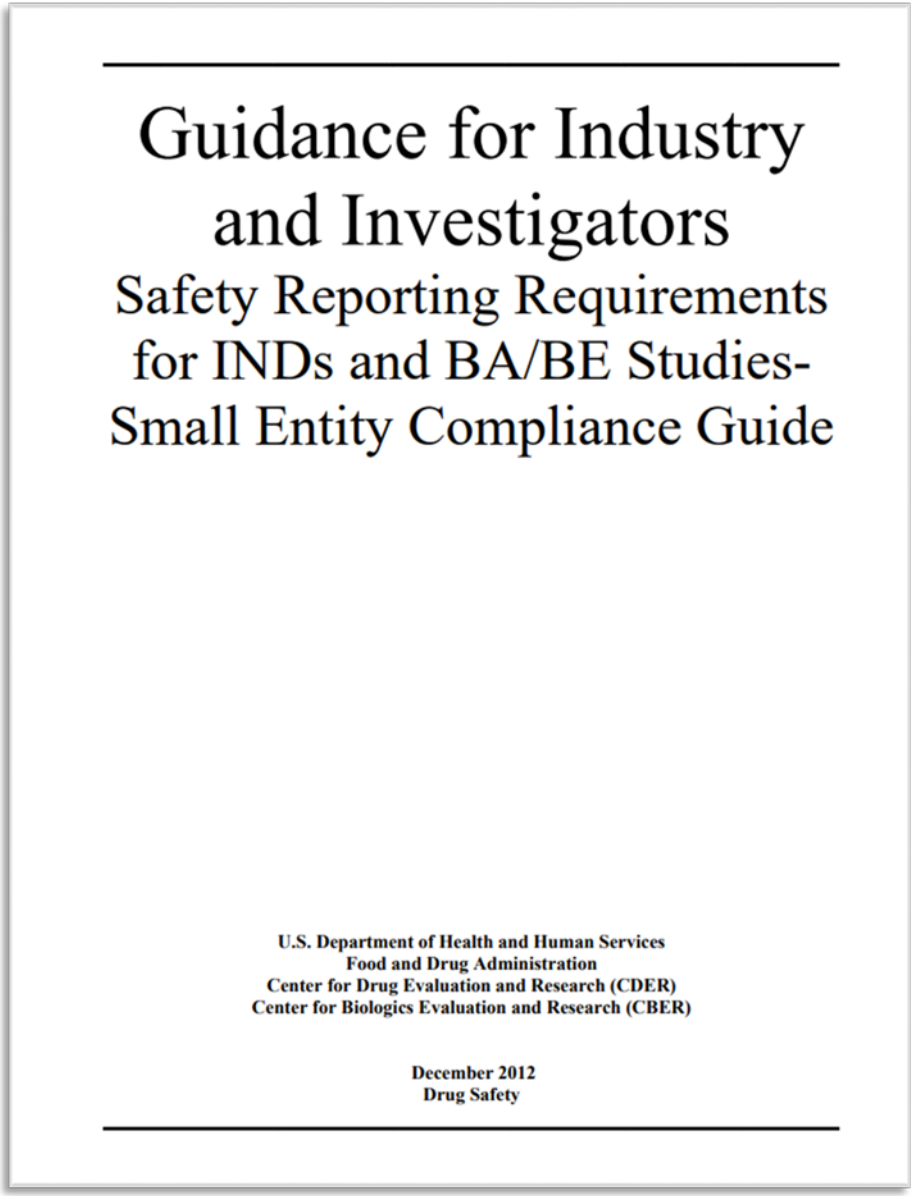
# 2020 New Draft Guidance:

## *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*

- **New draft guidance combines 2012 final and 2015 draft guidances**
  - **2015 draft guidance withdrawn now**



# 2012 Final Guidance Remains in Effect



Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies- Small Entity Compliance Guide

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2012
Drug Safety

# IND Safety Reporting Overview: What Does the 2010 Rule Address?

- **IND safety reports (21 CFR 312.32)**
  - ***Expedited*** **(7-day and 15-day) reports from the sponsor to FDA and all participating investigators**

- **Bioavailability/Bioequivalence safety reports (21 CFR 320.31(d))**
  - ***Expedited*** **reports from the person conducting the study to FDA and all participating investigators**

- **Investigator reports (21 CFR 312.64(b))**
  - **Reports from the investigator to the sponsor**
    - Topic to be covered in future guidance

# IND Safety Reports 15 and 7 Day

Reporting required **within 15 days** for:

- **Serious and unexpected suspected adverse reactions** (21 CFR 312.32(c)(1)(i))
- **Findings from other studies that suggest a significant risk in humans exposed to the drug** (21 CFR 312.32(c)(1)(ii))
- **Findings from animal and in-vitro testing** that suggest a **significant risk in humans** exposed to the drug (21 CFR 312.32(c)(1)(iii))
- **Increased rate of occurrence of serious suspected adverse reactions** (21 CFR 312.32(c)(1)(iv)), that, is of adverse reactions already thought to be drug-related.
- **Serious adverse events from bioavailability and bioequivalence** studies not under IND (21 CFR 320.31)

**IF unexpected fatal or life-threatening suspected adverse reactions THEN reporting required within 7 days of submission** (21 CFR 312.32(d)(3))

# Types of IND Safety Reports

## Individual Events

**Events that are:**

- **Uncommon and strongly associated with drug exposure (e.g., SJS)** (312.32(c)(1)(i)(A))
- **Not commonly associated with drug exposure but uncommon in population (e.g., tendon rupture)** (312.32(c)(1)(i)(B))

## Aggregate Analysis

**Events/findings that:**

- **Occur more frequently in drug treatment group than control** (312.32(c)(1)(i)(C))
- **Occur at a clinically important increased rate above that listed in protocol or IB** (312.32(c)(1)(iv))
- **Are identified in epidemiological studies, or pooled analysis of multiple studies, that suggest a significant risk** (312.32(c)(1)(ii))

# 2020 Draft Guidance

***SPONSOR RESPONSIBILITIES—SAFETY REPORTING REQUIREMENTS AND SAFETY ASSESSMENT FOR IND AND BIOAVAILABILITY/BIOEQUIVALENCE STUDIES***

INCORPORATING FEEDBACK FROM
THE 2015 DRAFT GUIDANCE
WITH UPDATED RECOMMENDATIONS

# Reporting Generally

**2020 Draft Guidance** expands on reporting requirements overall from the 2010 Rule. Of note:

- Before submitting an IND safety report, the sponsor needs to ensure that the event meets three criteria: (1) it is serious, (2) it is unexpected, i.e., not listed in the investigator's brochure, **and** (3) there is evidence to suggest a causal relationship between the drug and the adverse event (i.e., it is a suspected adverse reaction).
- **If the adverse event does not meet all three criteria, it should not be submitted as an IND safety report**
- **Sponsor should submit an IND safety report *only* when the *sponsor* determines that there is a reasonable possibility that the drug caused the event.**

# Overview of Aggregate Data Analyses

- Analyses of aggregate data is required to meet the reporting requirements under §§ 312.32(c)(1)(i)(C) or (c)(1)(iv)
- Aggregate analyses are needed to detect imbalances of adverse events across treatment arms
- Given the multiple events being examined and the relatively low rates of many adverse events, "statistical significance" is not the reporting threshold. **Non-statistically significant imbalances need to be considered**, and interpretation may require a broad evaluation including detailed assessment of trial data such as:
  - time to event, detailed case assessments, and reliance on information outside of the trial (pharmacology of the drug, class effects, and non-clinical findings)
- **2020 Draft Guidance** discusses considerations, methods, and approaches to conducting aggregate analyses

# Aggregate Analysis Considerations

- **Aggregate review** of anticipated events, that is, adverse events that are expected to occur in people with the disease being studied or in the population being studied independent of the disease, is more likely to detect an imbalance when drug development programs have **sufficient data** and **enrolled subjects** (e.g., late-stage)
  - More challenging to make meaningful comparisons of event numbers or to identify clinically important increase in event rate in small programs (sponsor may need to assess on an individual case basis)
- **Aggregate analyses** may be most useful in evaluating an **increased rate of relatively common events**, such as stroke or heart attack in an elderly population
- **Tailor approach** for implementing aggregate analysis based on disease and types of events while acknowledging that more than one approach may be plausible

# Aggregate Analyses: Determining Rates of Anticipated Events and Reporting Thresholds

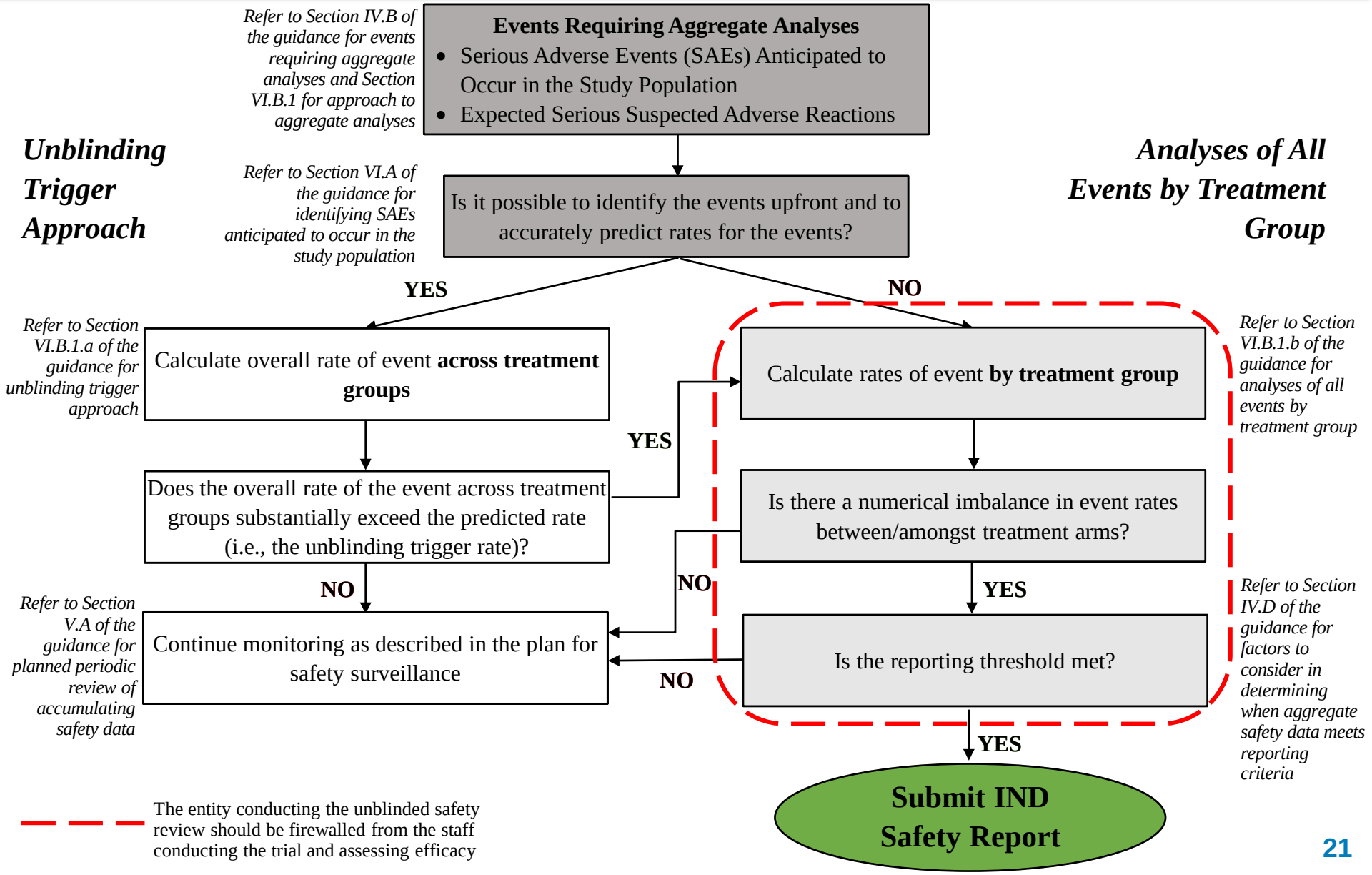
- **2020 Draft Guidance** makes recommendations on determining rates of adverse events and reporting thresholds under §§ 312.32(c)(1)(i)(C) or (c)(1)(iv)):
  - FDA recognizes that these determinations can be difficult and require clinical judgment. It is important for the sponsor to document reasoning:
    - Per the **2020 Draft Guidance**: "FDA will focus on the sponsor's **process and reasoning** underlying the sponsor's decision in the event the FDA and sponsor reach different conclusions regarding whether SAEs evaluated by analyses of aggregate data meets IND safety reporting criteria."

# Approaches to Aggregate Analyses

| Unblinding Trigger | Analyses of All Events by Treatment Group |
| --- | --- |
| • Prespecify predicted rates for anticipated SAEs<br>• IF rate of events in pooled treatment groups substantially exceeds pr… unblind fo…<br>• Compare e… if IND safe… are met<br>• Preferred … maintaining trial integrity if rates of anticipated SAEs can be accurately predicted | • Alternative approach where anticipated SAEs cannot be accurately predicted<br>• Conduct periodic aggregate … SAEs across … a numerical … further evaluation to determine if IND safety reporting criteria are met |

**Not mutually exclusive – Can combine approaches for different events**

# Flowchart: Appendix C
# Two Approaches to Aggregate Analyses



# Aggregate Analyses: Trigger Approach Determining Rates of Anticipated Events

- **2020 Draft Guidance: Trigger Approach**
  - **Recommends that estimates of predicted rates of events leverage all available data – placebo databases, historical controls, and real-world data**
  - **FDA recognizes challenge in predicting rates of anticipated events**
    - **Sponsors can predict rates of certain anticipated events and not others**
  - **Recommends that sponsors document rationale**

# Aggregate Analyses: Pooling Data Across Studies

**New Draft Guidance addresses concerns:**

- **Clinical and statistical judgments are needed to evaluate the totality of the information related to a specific AE**
  - **This includes information from trials in different populations, and study designs (e.g., different dosing schedules, durations of follow-up, and indications)**
- **FDA recognizes that these differences between studies may make it difficult to compare event rates across trials and documentation of this clinical assessment is recommended**
  - **The 2018 draft guidance for industry, Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products provides principles that can be applied to safety analyses that require combining data for multiple trials**

# Aggregate Analyses: Reporting Thresholds

**2020 Draft Guidance** describes reporting thresholds to interpret imbalances in aggregate data (once unblinded)

- Clinical and statistical expertise may be needed to consider factors such as:
  - Extent of the increase in incidence in test group compared to control group(s) [New]
  - Evidence of a dose response
  - Temporal relationship [New]
  - The consistency of the increase in multiple trials
  - The presence of a plausible mechanism of action
  - Nonclinical evidence to support the finding
  - Pharmacology of the drug (including receptor, transporter, or enzyme binding or activation studies and animal models) and known class effects [New]
  - Pattern across the study population (e.g., the event is observed more frequently in patients likely to be susceptible to the event) [New]
  - Occurrence of other potentially related adverse events (e.g., both strokes and transient ischemic attacks)

# Flexibility in Who Should Review Safety Information for IND Safety Reporting

**2020 Draft Guidance addresses stakeholder input:**

- **Starts with a statement that DMC may be used to conduct aggregate analysis**
  - Acknowledges modification to charter may be necessary
- **No longer calls the entity a Safety Assessment Committee**
  - If the sponsor does not use a DMC, should identify an entity within the sponsor's organization that would evaluate safety information for the development program if appropriate firewalls could be maintained for review of unblinded data
- **Adds flexibility regarding the size (individual or group), background, internal and external members**

# Entity(ies) that Reviews Aggregate Data

- **2020 Draft Guidance addresses comments from 2015 guidance and no longer recommends using a safety assessment committee (still recommends that a formalized entity should monitor safety).**

- **New recommendations include:**
  - Sponsor may choose to designate an entity (an individual or group of individuals) to review the accumulating safety information in a drug development program to make a recommendation to the sponsor regarding whether the safety information meets reporting requirements
  - Sponsors have flexibility in determining which entity(ies) should perform this function
  - Discusses composition of the reviewing entity(ies)
  - Describes process and considerations for using a DMC to conduct aggregate analyses
  - Describes steps used to protect trial integrity during aggregate analyses

# Use of DMC to Review Aggregate Data

**2020 Draft Guidance indicates that a DMC, if in place, may be used to conduct aggregate analysis. It discusses some considerations when using a DMC:**

- DMC may use existing controls for maintaining trial integrity, despite their access to unblinded data
- DMC could review the accumulating safety data collected over time in late stage drug development and across multiple trials, across INDs for the particular drug, and from other sources, if applicable, and assessing whether the IND safety reporting criteria have been met
- If DMC is used to review aggregate data then the DMC charter should reflect this role

# Unblinding of Safety Data and Implications for Trial Integrity

**2020 Draft Guidance addresses concerns:**

- **No longer generally recommends regular unblinding for comparison of event rates as the preferred method**
- **Acknowledges that the "trigger approach" based on pooled results is acceptable**
  - Sponsors' comments on the 2015 draft noted this approach
- **Recommends unblinded analysis by treatment group in certain circumstances. May be useful:**
  - When not possible to accurately predict rates of anticipated SAEs
  - For events that are not initially identified as anticipated

# Unblinding of Safety Data and Implications for Trial Integrity (2)

**2020 Draft Guidance updates:**

- **Regular unblinding replaced with:** Aggregate data review of pooled data at intervals based on volume of safety data collected or subject accrual, in the absence of a specific concern. **For example, every 6 months or more frequently as appropriate.**
  - Recommends that safety surveillance plan describe frequency of review and the rationale behind it the frequency
- If unblinding, **adequate firewalls** are required between staff performing the safety review and staff conducting the study and assessing efficacy

# Safety Surveillance Plan

**2020 Draft Guidance recommends:**

- **Safety surveillance (monitoring) plan should be maintained by the sponsor and must be available for FDA inspection**
- **Eliminates need to submit to IND but indicates that it must be available upon FDA request**
- **Sponsors may discuss the anticipated SAEs with the review division during protocol development and prior to trial initiation, as appropriate**

# Clarifies IND Safety Reporting for Marketed Drugs and Active Control

## 2020 Draft Guidance:

- **Expands on position in 2012 final guidance**
- **Suspected adverse reaction to a control drug that is both serious and unexpected should be assessed and reported as individual events**
  - Aggregate analysis is not required for these events, as the applicant (e.g., NDA or BLA holder) is better positioned to perform such analyses than the IND sponsor
- **Sponsor should consider sharing reports of adverse events of a marketed or approved drug to the corresponding NDA or BLA holder**
- **The sponsor should also consider sharing events that suggest a higher rate with the active control group with the NDA or BLA holder even if they do not rise to the level of IND safety reporting**

# NEW: Streamlining Electronic Reporting Using ICH E2B Standards

# IND Safety Reports – Electronic Submission Process

| Old Electronic Process: PDFs in eCTD format | New Process: ICH E2B XML files to FAERS |
|---|---|
| • Inefficient and labor intensive review<br>• Lack of universal tracking system | • Allows for use of data visualization and analytic tools for review and tracking<br>• Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway)<br>• Complies with existing federal regulations 21 CFR 312.32(c)(1)(v) |

# Requirements and Timelines

**Required change in format under 745A(a) of FD&C Act**

- **Sponsors of commercial INDs will be required to submit certain IND safety reports* to FAERS by one of two methods:**
  - **Electronic Submissions Gateway (ESG)**

    **or**
  - **Safety Reporting Portal (SRP)**
- **Requirement effective 24 months after publication of final guidance: *Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry*; voluntary submissions from all sponsors will be accepted and encouraged prior to requirement**

**FDA will announce when the voluntary submission process will begin. FDA highly encourages sponsors of all INDs, both commercial and noncommercial, to begin submitting IND safety reports to FAERS voluntarily as soon as the new submission process is available.**

*Serious and unexpected suspected adverse reactions that contain individual patient data

# Other Guidance and Information Regarding Electronic Submission of IND Safety Reports

- ***Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry (October 2019)***
- ***Electronic Submission of IND Safety Reports - Technical Conformance Guide (October 2019)***
- ***Revised Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments (February 2020)***
- **FAERS website recently updated with links the Guidance and technical specification documents specific to IND safety reports**
- **FDA will soon announce when sponsors can begin to voluntarily submit IND safety reports to FAERS**

# Appendix A

## Flowchart for Determining Whether an Adverse Event Meets Criteria for IND Safety Reporting to FDA

*Refer to section III.D of the guidance and 21 CFR 312.32(a) for definition of "serious"*

**Is the AE serious (as assessed by either the investigator or sponsor)?**

NO → Include the AE in an annual report (see 21 CFR 312.33) or an information amendment to the IND (see 21 CFR 312.33), as appropriate.

YES ↓

*Refer to Section III.C of the guidance and 21 CFR 312.32(a) for definition of "unexpected"*

**Is the SAE unexpected (*as assessed by the sponsor*)?**

YES → **Is there a reasonable possibility that the drug caused the SAE (as assessed by the sponsor)?**

Examples of evidence suggesting a causal relationship between the drug and the SAE include

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (i.e., 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 (i.e., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug exposure) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

*Refer to Section III.B of the guidance and 21 CFR 312.32(a) for definition of "suspected adverse reaction," and Section III.B of the guidance and 21 CFR 312.32(c)(1)(i) for examples of evidence which suggest a causal relationship between the drug and the SAE*

YES → **Submit IND safety report**

NO → Include the SAE in an annual report (see 21 CFR 312.33) or an information amendment to the IND (see 21 CFR 312.33), as appropriate.

NO → **Does the expected SAE indicate a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator's brochure?**

YES → **Submit IND safety report**

NO → Include the SAE in an annual report (see 21 CFR 312.33) or an information amendment to the IND (see 21 CFR 312.33), as appropriate.

AE = adverse event
SAE = serious adverse event

# Additional Information

**Submitting Comments on Draft Guidance:**

- You may submit comments at any time
- Submit comments electronically through Federal eRulemaking Portal (www.regulations.gov)
- Submit written comments to Documents Management Staff at FDA
- More information on submitting comments can be found in the Notice of Availability for this draft guidance (ADD LINK)

**Resources:**

- FDA IND Safety Reporting Website (https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports)
- *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies:* (ADD LINK)

**Questions:**

- Email: CDEROMP@fda.hhs.gov
- Phone: 301-796-2500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