



CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

***Managing Safety Data in Multi-
Regional Trials (and Beyond)***

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Agenda

- ▶ **Relevant Regulations and Guidances**
- ▶ **Establishing a Safety Profile**
- ▶ **Defining Expected Events in the Protocol**
- ▶ **SUSARs**

Ethical and Regulatory Responsibilities

- ▶ **Declaration of Helsinki**
 - “The health of my patient will be my first consideration.”
- ▶ **ICH Tripartite Guideline on Clinical Safety Data Management (ICH E2A) (issued on October 27, 1994)**
- ▶ **ICH Tripartite Guideline on Good Clinical Practice (ICH E6) (issued on June 10, 1996)**
 - 4.11 – Safety Reporting by Investigator
 - 5.17– Adverse Drug Reaction Reporting by Sponsor
 - 6.8 – Protocol – Assessment of Safety
- ▶ **Volume 10 Clinical Trials Guidelines and CTD CT-3**
 - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) 2011/C 172/01
- ▶ **US FDA Regulations**
 - *Pre-marketing: 21 CFR 312.32*
 - Post-marketing: 21 CFR 314.80
 - *21 CFR 314.81*

Safety Profile not Fully Established during Development

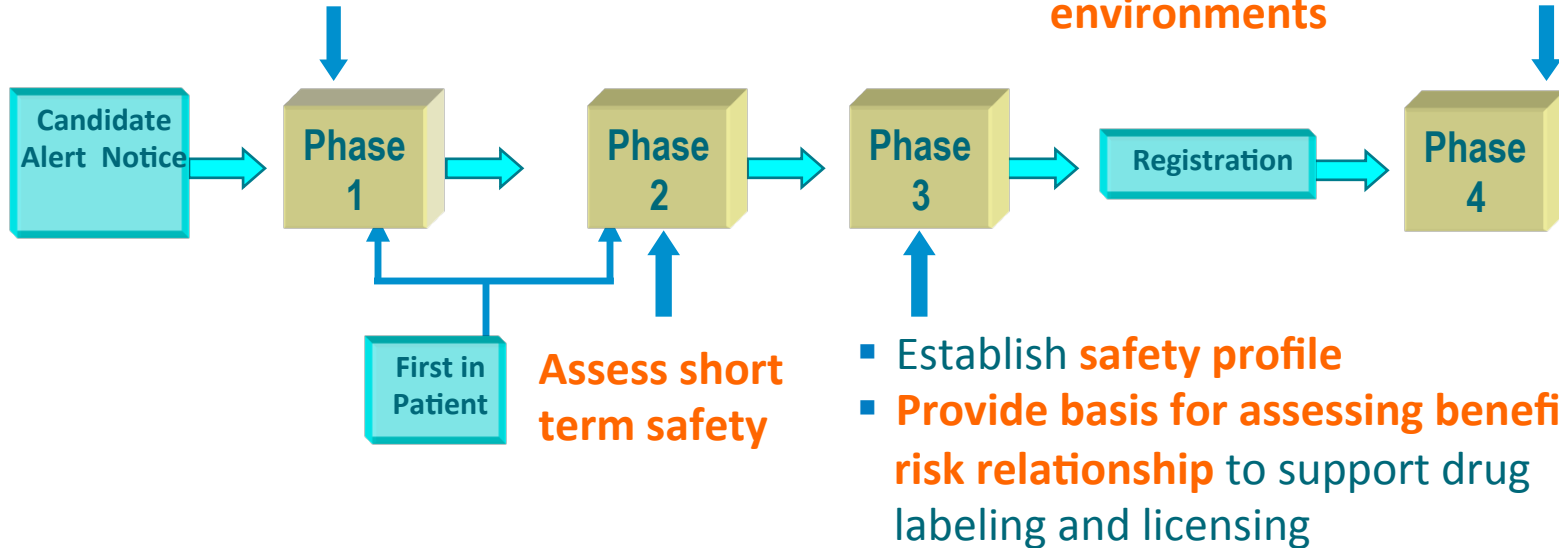
- ▶ ***Therefore:***
- ▶ ***“The sponsor should continuously weigh anticipated benefits and risks of the clinical trial, which includes ongoing safety evaluation of Investigational Medicinal Products”¹***
- ▶ ***“The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsor shall make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32...”²***

¹Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) 2011/C 172/01 and Article 3(2)(a) of Directive 2001/20/EC.

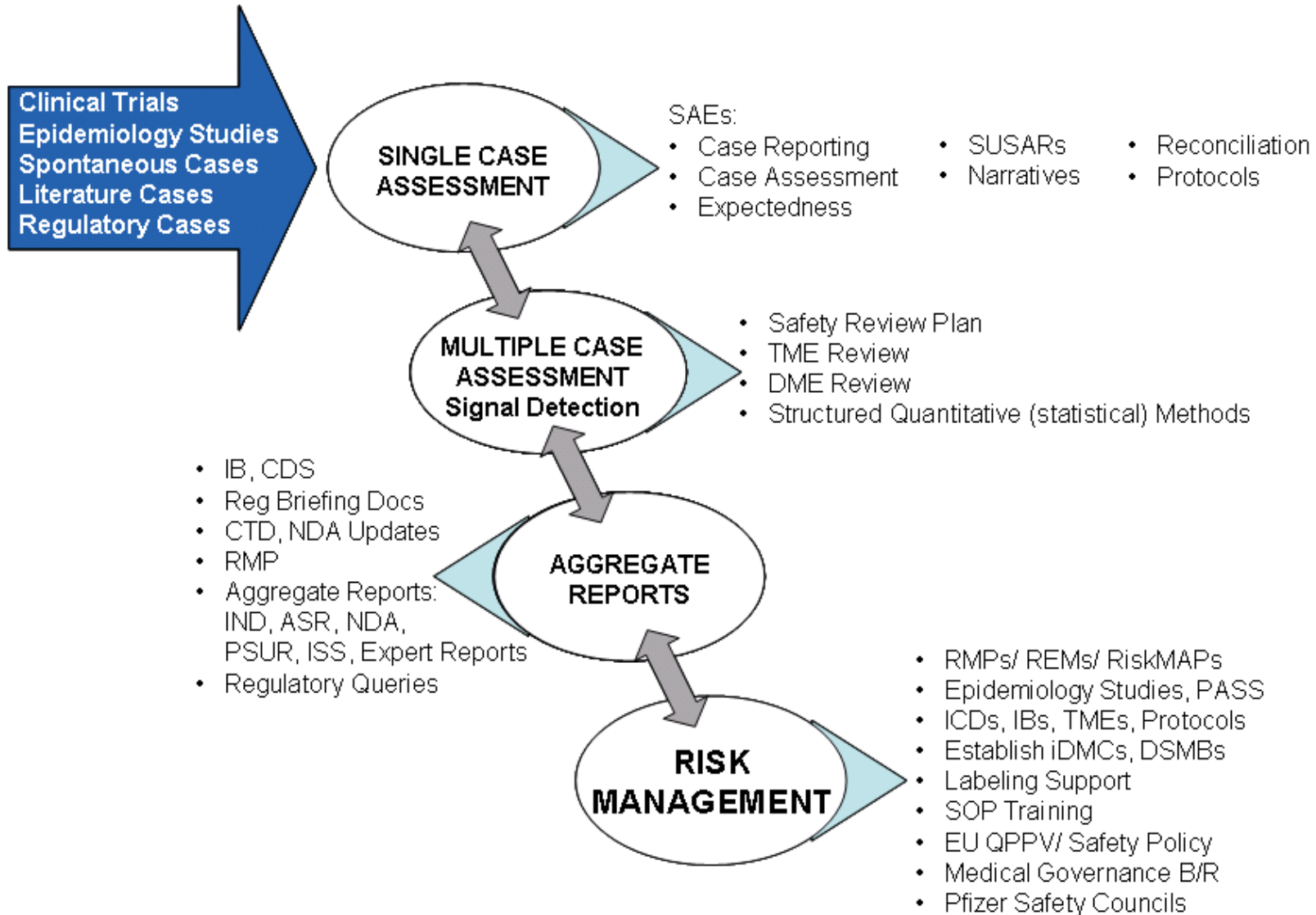
Assessing Safety of Investigational Drugs

- Preliminary evaluation of the drug's safety
- **Theoretical risks** based on pre-clinical studies and clinical **mechanisms of action**

**Refine understanding of benefit/
risk relationship in general or
special populations and/or
environments**

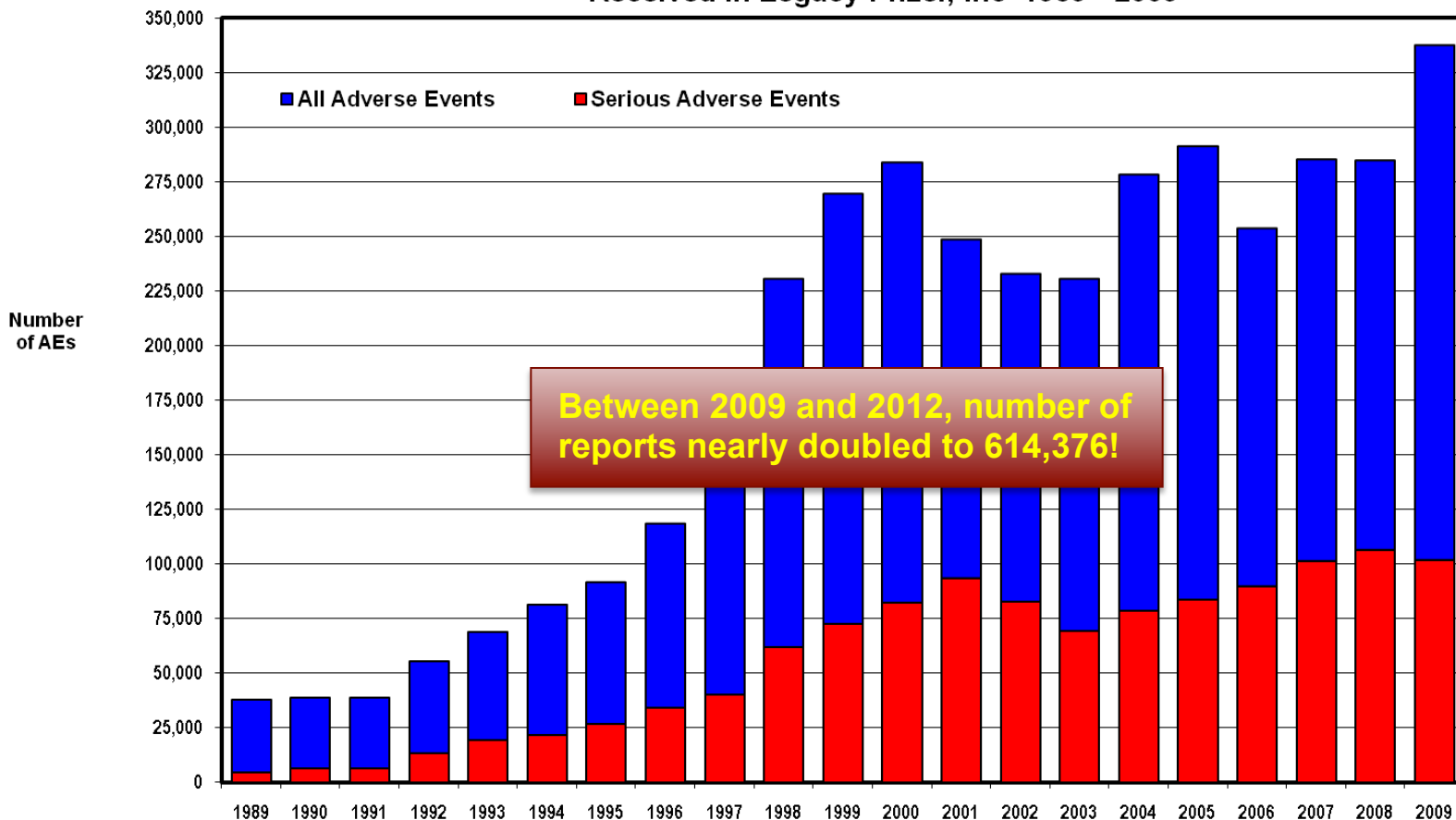


Post Marketing Safety Assessments



Number of Safety Reports is Growing at a Near-Exponential Rate

Serious Adverse Events / All Adverse Events in Individual Case Safety Reports Received in Legacy Pfizer, Inc 1989 - 2009



Circumstances in Which Targeted Data Collection May be Appropriate*

- ▶ **Although it is reasonable and appropriate to limit collection of additional data on well-characterized adverse events and certain other types of safety data, it is also important not to compromise the ability to identify important new safety problems (new serious events or events more prominent in a new population) or to start selective data collection before the safety profile of the drug has been adequately characterized at the doses being studied. In general, selective or specifically targeted safety data collection is appropriate when the following conditions are present:**
 - ▶ The number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events
 - ▶ The occurrence of adverse events has been generally similar across multiple studies
 - ▶ There is a reasonable basis to conclude that occurrence of adverse events in the population to be studied will be similar to previously observed rates

HABP / VABP Guidance: Safety Considerations*

- ▶ **The protocol should specify the methods to be used to obtain safety data during the course of the trial. *Both adverse event information and safety laboratory data should be collected. All patients should be evaluated for safety at the time of each visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.***
- ▶ A sufficient number of patients, including patients older than 65 years and patients with renal impairment, should be studied at the dose and duration proposed for use to draw appropriate conclusions regarding drug safety. Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for HABP/VABP. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be needed based on the nonclinical and clinical profile of the specific drug under investigation. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial should be considered, depending on the specific drug's potential for long-term or delayed adverse effects.

*Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, Draft Guidance, November, 2010.

www.ctti-clinicaltrials.org



IND Safety Final Rule: Federal Register discussion by FDA*

- ▶ The agency agrees with the comments recommending that at the time of protocol development the sponsor identify the serious adverse events (i.e., known consequences of the disease or those otherwise common in the study population) that it plans not to report individually in an expedited manner but that it will monitor during the course of the trial.
- ▶ FDA encourages use of this process. ***Should an aggregate analysis indicate that those events occur more frequently in the drug treatment group, the sponsor must then report that information in an IND safety report under § 312.32(c)(1)(i).***
- ▶ However, the agency recognizes that it is not possible, nor desirable, to list in the protocol every adverse event that may be anticipated to occur in the study population; **the protocol should therefore limit such a list to those events that are common, even in the absence of drug exposure.** For example, in a longterm osteoporosis trial in an elderly population, it would be reasonable to list myocardial infarction, but unreasonable to list acute narrow angle glaucoma—an event that can occur in this elderly population, but is relatively rare.

SUSARs: FDA Investigator Responsibilities

- ▶ § 312.64 Investigator reports.

- ▶ * * * * *

- ▶ **(b) *Safety reports.*** *An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.*

SUSARs: FDA Sponsor Responsibilities

- ▶ **The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:**
 - ▶ A 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 (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 therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

SUSARs as Defined under CT-3

7.2. Suspected unexpected serious adverse reaction

7.2.1. 'Adverse reaction' — causality

- ▶ 43. An 'adverse reaction' is defined in Article 2(n) of Directive 2001/20/EC as follows:
'all untoward and unintended responses to an investigational medicinal product related to any dose administered'.
- ▶ 44. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
- ▶ 45. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.
- ▶ 46. An untoward and unintended response to a non-IMP which does not result from a possible interaction with an IMP is, by definition, not a SUSAR (see also section 7.6). For possible follow-up action reference is made to section 7.11.3.
- ▶

Causality Assessments and CT-3

▶ 7.3.2. *Causality*

58. The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator.

59. In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. **The causality assessment given by the investigator should not be downgraded by the sponsor.** If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

CT-3: What needs to be reported?

▶ **14. The investigator's responsibilities entail:**



— *reporting of serious adverse events to the sponsor (see section 4),*

— *reporting of certain non-serious adverse events and/or laboratory abnormalities to the sponsor (see section 5).*

▶ **The latter is in line with 2001/20EC Article 16(2)**

▶ *Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.*

Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') 2011/C 172/01

and

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities, 01 May 2001.

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EU CTD CT-3

Protocol Defined Events (paragraph 115)

- ▶ However, for trials in high morbidity or high mortality disease, **where efficacy end-points could also be SUSARs** or when mortality or another ‘serious’ outcome (that may potentially be reported as a SUSAR) is the efficacy end- point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, **the sponsor should reach agreement in the authorisation process as to which serious events would be treated as disease- related and not subject to systematic unblinding and expedited reporting (62).**

- ▶ ⁶²See section 2.5 of the detailed guidance CT-1.

Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) 2011/C 172/01

EU CTD CT-1 Section 2.5

- ▶ **With regard to notification of adverse events, the protocol**
 - may identify serious adverse events which do not require immediate reporting by the investigator (cf. Article 16(1) of Directive 2001/20/EC), and
 - shall identify adverse events or laboratory anomalies critical to safety evaluations to be reported to the sponsor (cf. Article 16(2) of Directive 2001/20/EC).

Directive 2001/20/EC

▶ Article 16(1) of Directive 2001/20/EC

- ▶ The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

▶ Article 16(2) of Directive 2001/20/EC

- ▶ Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

▶ Article 16(4) of Directive 2001/20/EC

- ▶ The sponsor shall keep detailed records of *all* adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities, 01 May 2001.

Conclusions

- ▶ **Until the safety profile of the investigational product is reasonably well established, systematic collection and appropriate reporting of all safety data ensures**
 - ▶ Safeguards for patients
 - ▶ Better understanding of drug's safety profile
 - ▶ Compliance with relevant regulations, some of which may not be completely aligned across regions
- ▶ **Once the safety profile is understood, US guidances point to potential limited safety data collection**
 - ▶ No similar guidances in the EU
 - ▶ When is the safety profile really understood?

▶ THANK YOU



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www.ctti.clinicaltrials.org

CT-3: What is it?

- **Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) issued on 11 June 2011**
- **CT-3 has its basis in Article 18 of the CT Directive (2001/20/EC) and sets out the European Commission’ s (EC) view regarding compliance with the legislation**
- **Scope of CT3, as defined by EC, is:**
 - This detailed guidance addresses the collection, verification and reporting of adverse events and adverse reactions which occur in a clinical trial falling within the scope of Directive 2001/20/EC, i.e. a clinical trial as defined therein and performed in at least one EU Member State.**

EU Guidance CT-3: Key Changes

Changes to:

- SAE/SUSAR collection, definition (relatedness, expectedness), reporting
- Reference Safety Information (RSI) definition
- Specifications for unblinding
- Specifications for other, non-SUSAR safety issues
- ASR replaced by DSUR

Commonalities with the US by the Final Rule, as regards:

- Abolition of the reporting of spontaneous reports as SUSARs when the product is investigational in the regulatory region and marketed elsewhere.
- Increased formalization of required ongoing safety evaluation during the study.
- Unblinded staff, independent from the study team, conducting safety analyses of the ongoing trial
- Reporting of safety concerns (confirmed adverse reaction = safety information leading to a substantial amendment)
- Possibility to exclude disease-related events from expedited reporting***

- ▶ **Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them (16).**