Safety Reporting In Cell Therapy Clinical Trials

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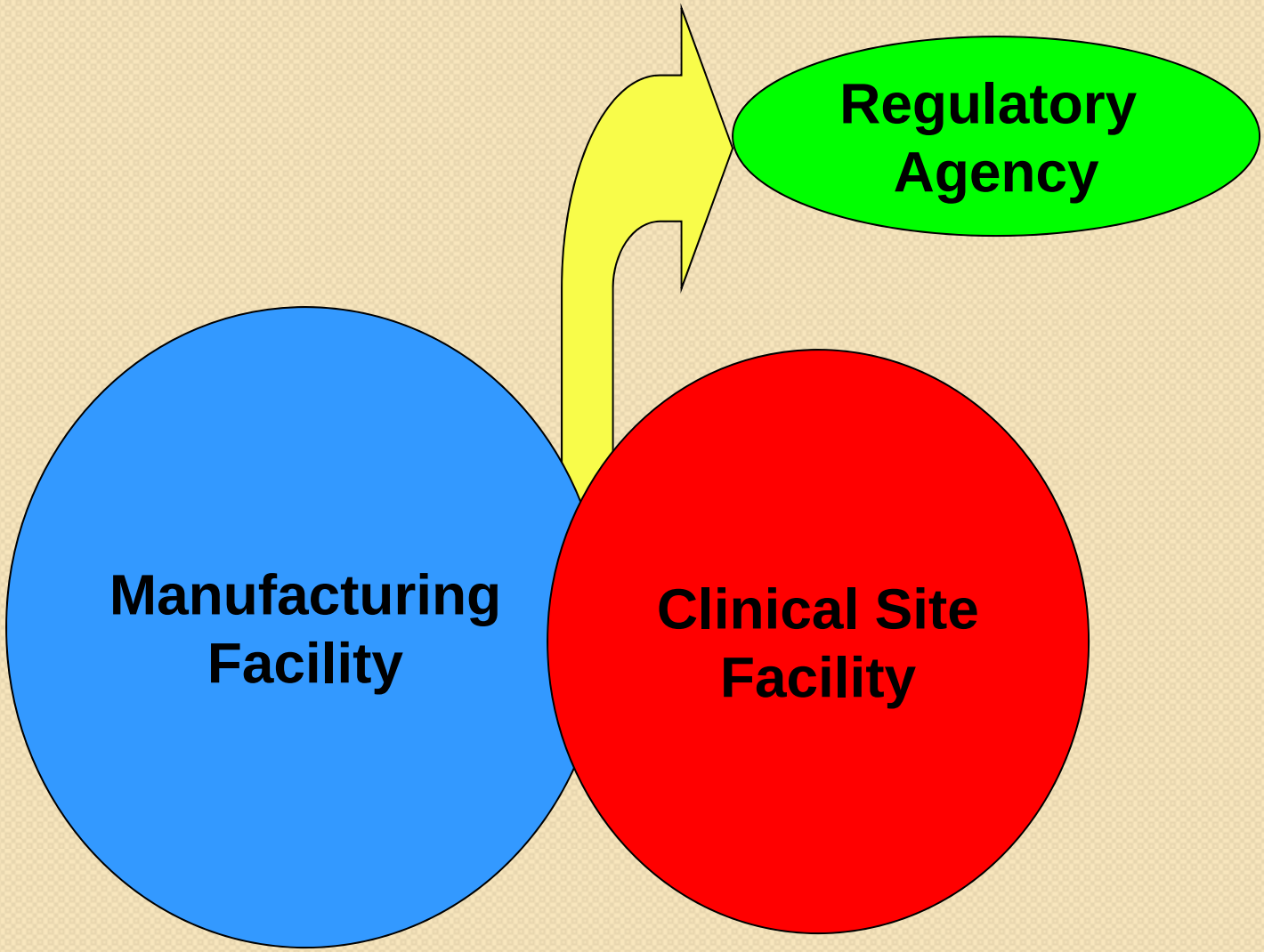
SAFETY
Who needs that?

Safety Reporting



Product Use

- Is this and IND study?
- Have you met with the clinical team?
- Does the clinical team understand your need to know about infusion reactions?
- Do you understand the need to inform the clinical team of manufacturing issues?

For IND Studies

Who is the IND Sponsor?

- Clinical Investigator
- Manufacturing Investigator
- Independent Company

Clinical Trial Team (Sponsor)

- Develop a research question
- Develop the measurements to answer that question
- Develop a protocol
- Develop safety reporting strategies
- Develop stopping rules
- Identify research sites
- Conduct the trial per protocol
- Review reported safety events
- Report the trial results

Clinical Site

- Provide medical care
- Take medical history
- Conduct physical exam
- Evaluate medical events
- Prescribe treatment
- Report adverse events

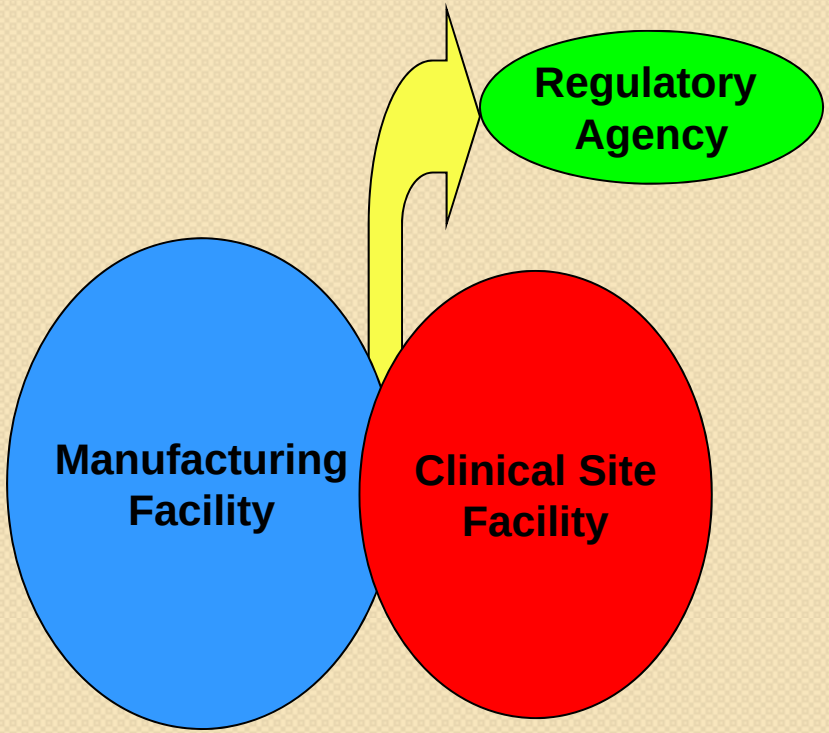
Manufacturing Facility

- Maintain GMP and GTP procedures
- Assess for Product Deviations
  - Collection, processing and infusion
    - Microbial contamination
    - Suspected disease transmission
    - During or after product administration

Regulatory Agency

- Identify safety risks
- Review protocol for safety reporting parameters
- Review manufacturing deviations
- Review all adverse events in annual report
- Review expedited reports when submitted
- Evaluate reported adverse events

Safety Reporting
Where is the Critical Piece?



Safety Reporting
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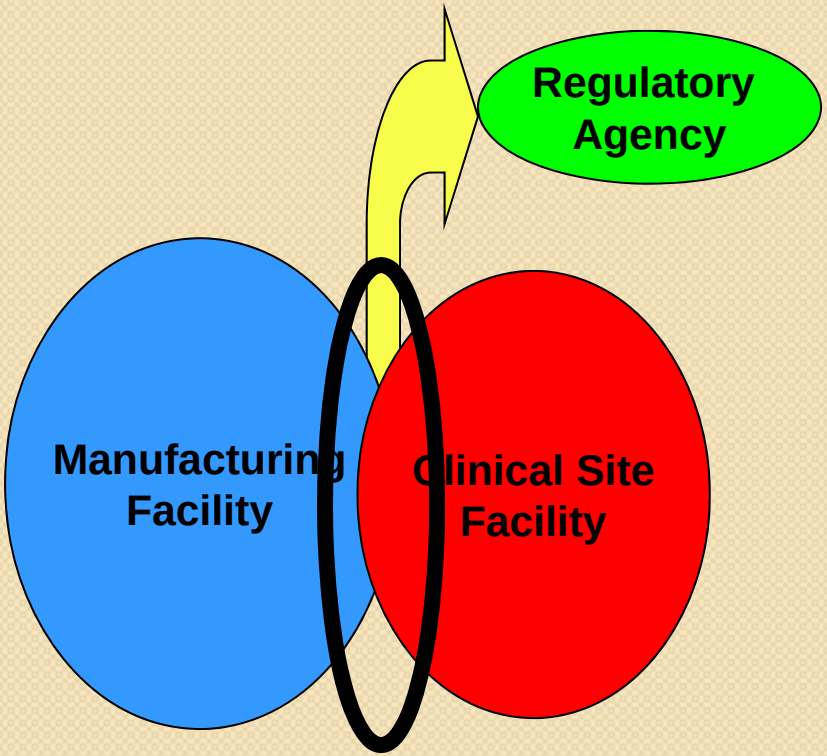

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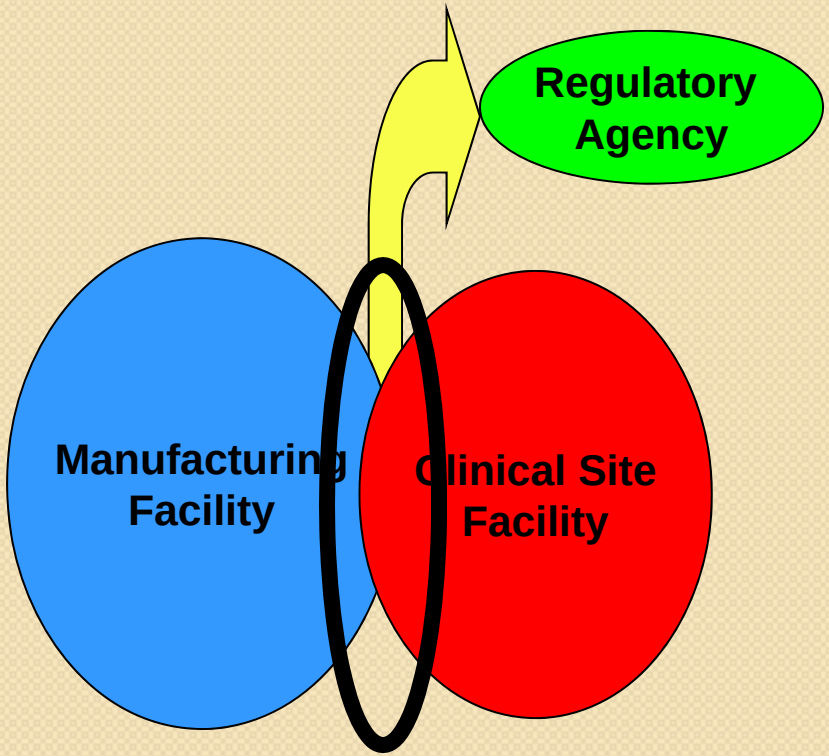


Communication between the Manufacturing Facility and the Clinical Site is critical to maintain the regulatory obligations of the IND

New FDA Regulations for Safety Reporting in INDs - Background

- March 14, 2003 - FDA issued proposed rule to revise its regulations governing pre and post marketing safety reporting for human drugs and biological products.
- 110 comments received from Manufacturers, Trade Representatives, CROs, Universities, etc.
- September 29, 2010 - FDA published a final rule amending safety reporting requirements for INDs and Bioavailability/Bioequivalence (BA/BE) Studies.
- September 2010 - Draft Guidance issued to address rule changes
- March 28, 2011- Final rule became effective
- September 28,2011 Final rule enforced

Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Janet Norden at 301-796-2500, or (CBER) Office of Communication, Outreach and Development at 301-827-1800 or 800-835-4709.

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)

September 2010
Drug Safety

FDA New Regulation/Guidance Clinical Trial Safety Reporting

- Major principles
  - Quit submitting useless individual safety reports
  - Quit calling things related unless there is evidence
  - Quit dumping all adverse events into investigator brochures
  - Sponsors need to think – make decision regarding expedited reporting
  - Protocol development of creative safety plans and reporting strategies

Definitions

- **Adverse event**

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

- **Suspected adverse reaction**

  Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there

  is evidence

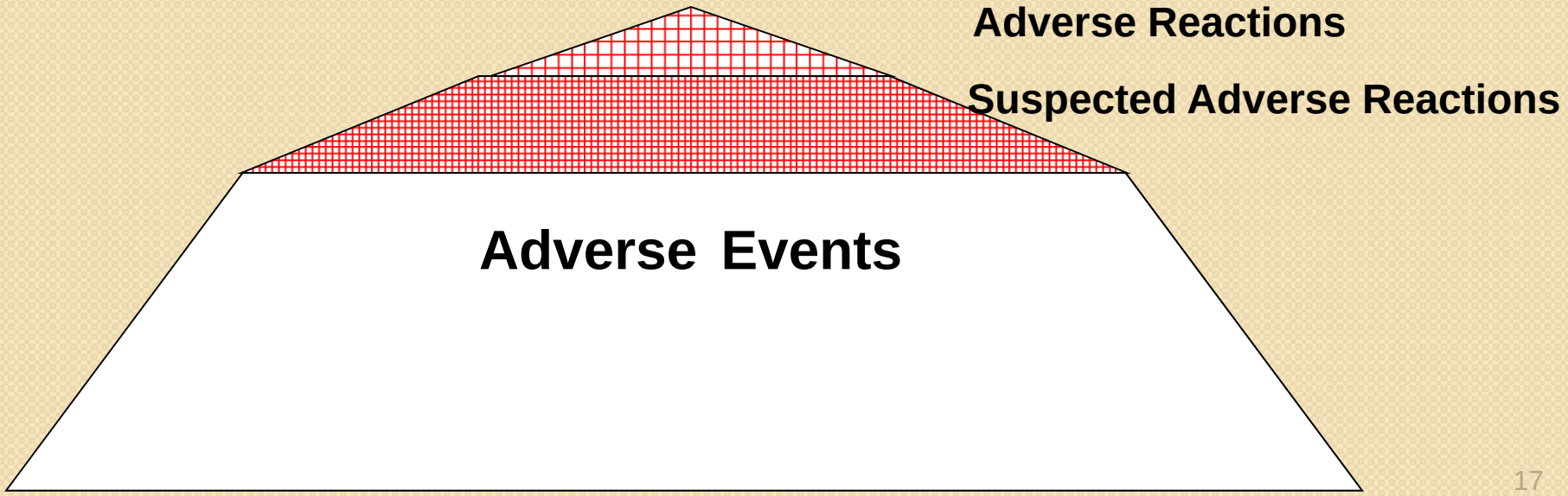
  to suggest a causal relationship between the drug and the adverse event.

- **Adverse Reaction**
  - Any adverse event caused by the drug

FDA New Regulation/Guidance

New Terms

- Adverse Event
- Suspected Adverse Reaction
- Adverse Reaction



Investigator Brochure

- Only include adverse events for which a causal relationship is suspected or confirmed
- Update the IB as new information becomes available
- Continue to report as unexpected until IB is updated

Previous – Lists any and all AEs reported

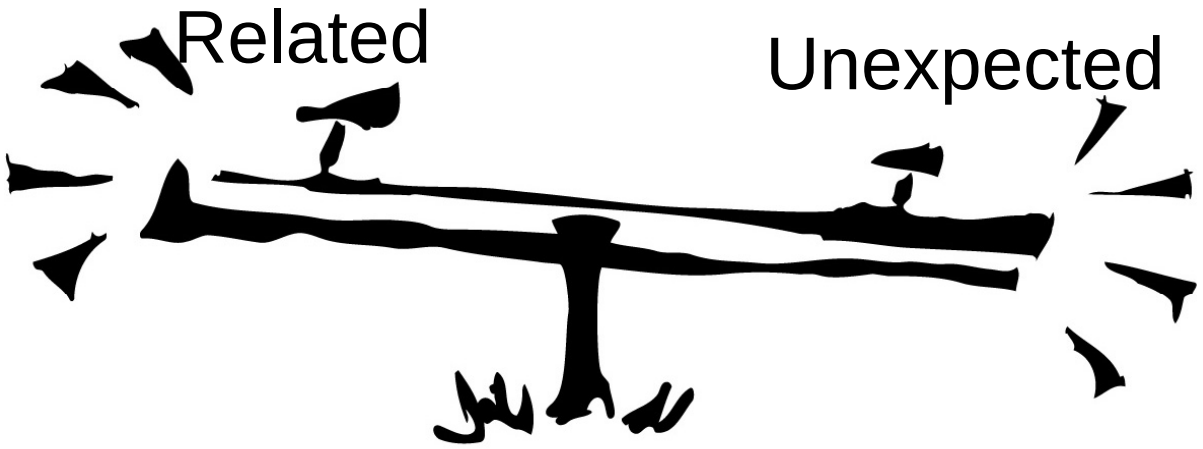
New – List only Suspected Adverse Reactions

Expedited Reporting

- The adverse event meets all three of the definitions contained in the requirement:
  - Suspected adverse reaction
  - Serious
  - Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

This has always been a balance for expedited reporting!



Expedited Reporting

- Only sponsor can make this determination if it meets the definition of expedited reporting
- Sponsor OR Investigator determines SERIOUSNESS
- Sponsor decides RELATIONSHIP
- Sponsor decides EXPECTDEDNESS
- Sponsor will investigate and document its decisions
- Timeline starts when there is adequate information to determine relationship and expectedness

Operational Issues
Guidance Document

- **Unblinding**
  - Any event that requires expedited reporting
  - If in Placebo group-would not be reported as an expedited report
  - If in Treatment group-would be reported as an expedited report
  - If unblinding individual events would compromise the study an alternative method can be proposed by the sponsor

MedDRA Coding

- **MedDRA - the Medical Dictionary for Regulatory Activities**
  - medical terminology used to classify adverse event
  - coding allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products.

- **MedDRA was developed by the International Conference on Harmonisation (ICH)**

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MedDRA Coding

MedDRA Structure

System Organ Class (SOC) (26)

High Level Group Term (HLGT) (335)

High Level Term (HLT) (1,709)

Preferred Term (PT) (18,786)

Lowest Level Term (LLT) (68,258)

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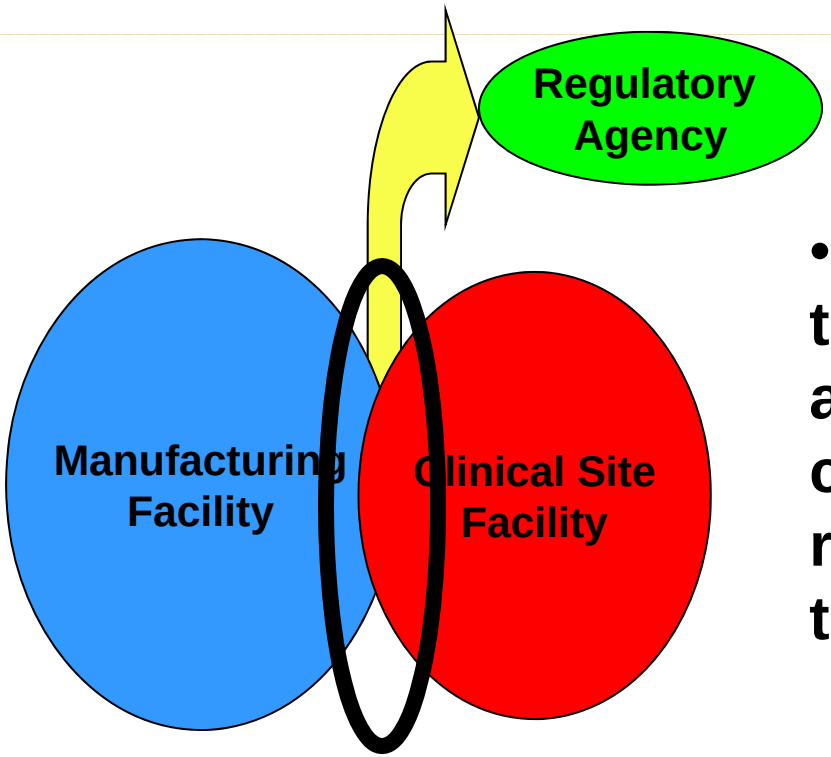
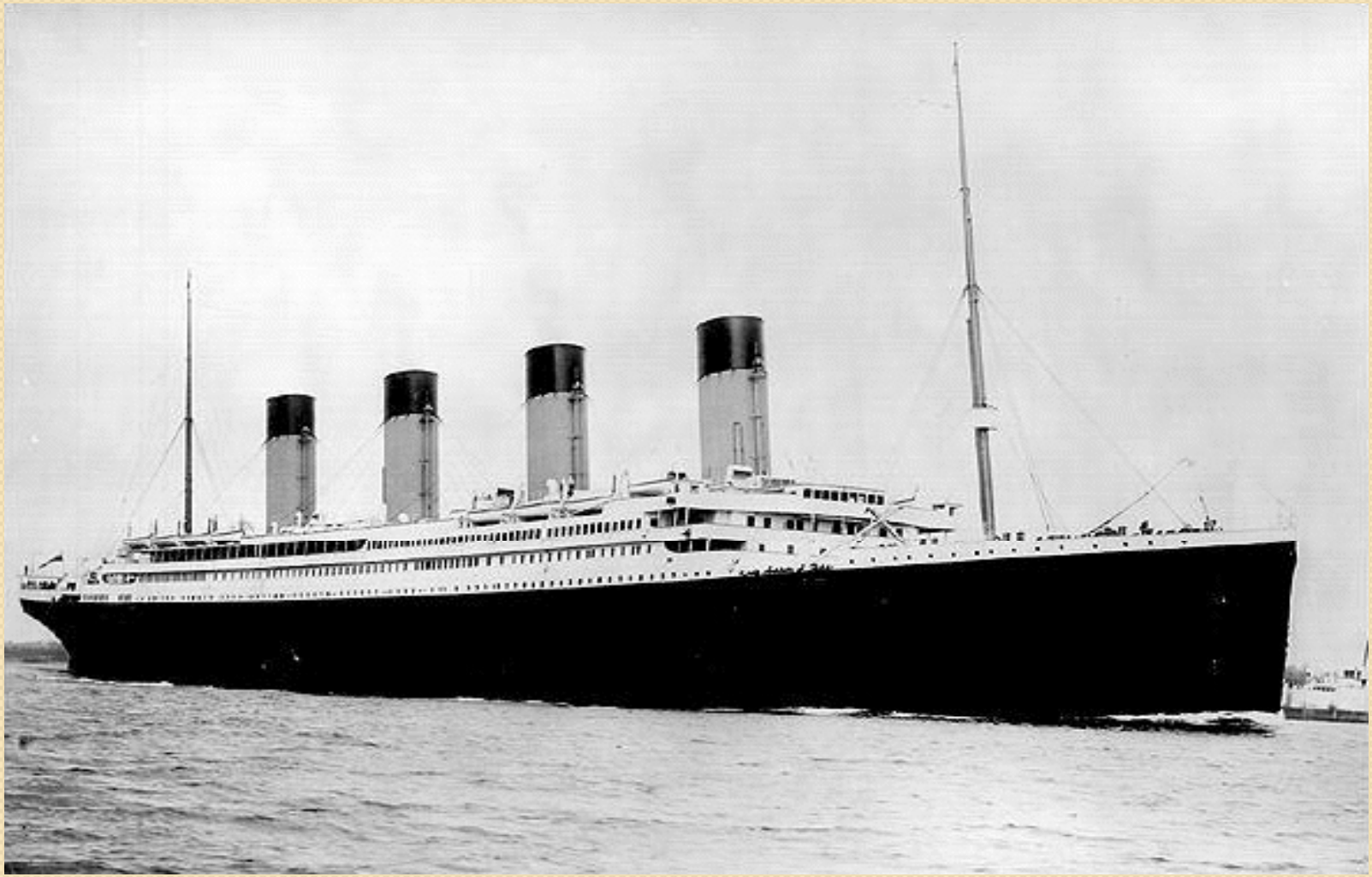
In Summary-

- **Know the new Regulations and Guidance documents**



- **Communication between the Manufacturing Facility and the Clinical Site is critical to maintain the regulatory obligations of the IND**

Importance of Safety Reporting



Importance of Safety Reporting