

# *Data Reliability – BA/BE Inspections and Global Collaboration*

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## Disclaimer

The contents of this presentation are of my own and do not represent views or policies of the U.S. Food and Drug Administration

# OBJECTIVES

- Understand the CDER Bioavailability and Bioequivalence compliance program's evaluation of testing site study conduct
- Understand some of the critical and complex international collaboration that occurs to assure Bioavailability and Bioequivalence study oversight

# AGENDA

1. Bioresearch Monitoring (BIMO)  
- CDER OSIS BIMO Program
2. BA/BE Study Conduct Expectations
3. Data Integrity
4. Data Integrity – Case Example
5. Data Integrity – BA/BE International Collaboration

# CDER BIMO PROGRAM OBJECTIVES

- To protect the rights, safety, and welfare of human research subjects
- To verify the accuracy, reliability, and integrity of clinical and non-clinical trial data submitted to FDA
- To assess compliance with FDA's regulations governing the conduct of clinical and non-clinical trials, including regulations for informed consent and ethical review

# OSIS BIMO PROGRAM

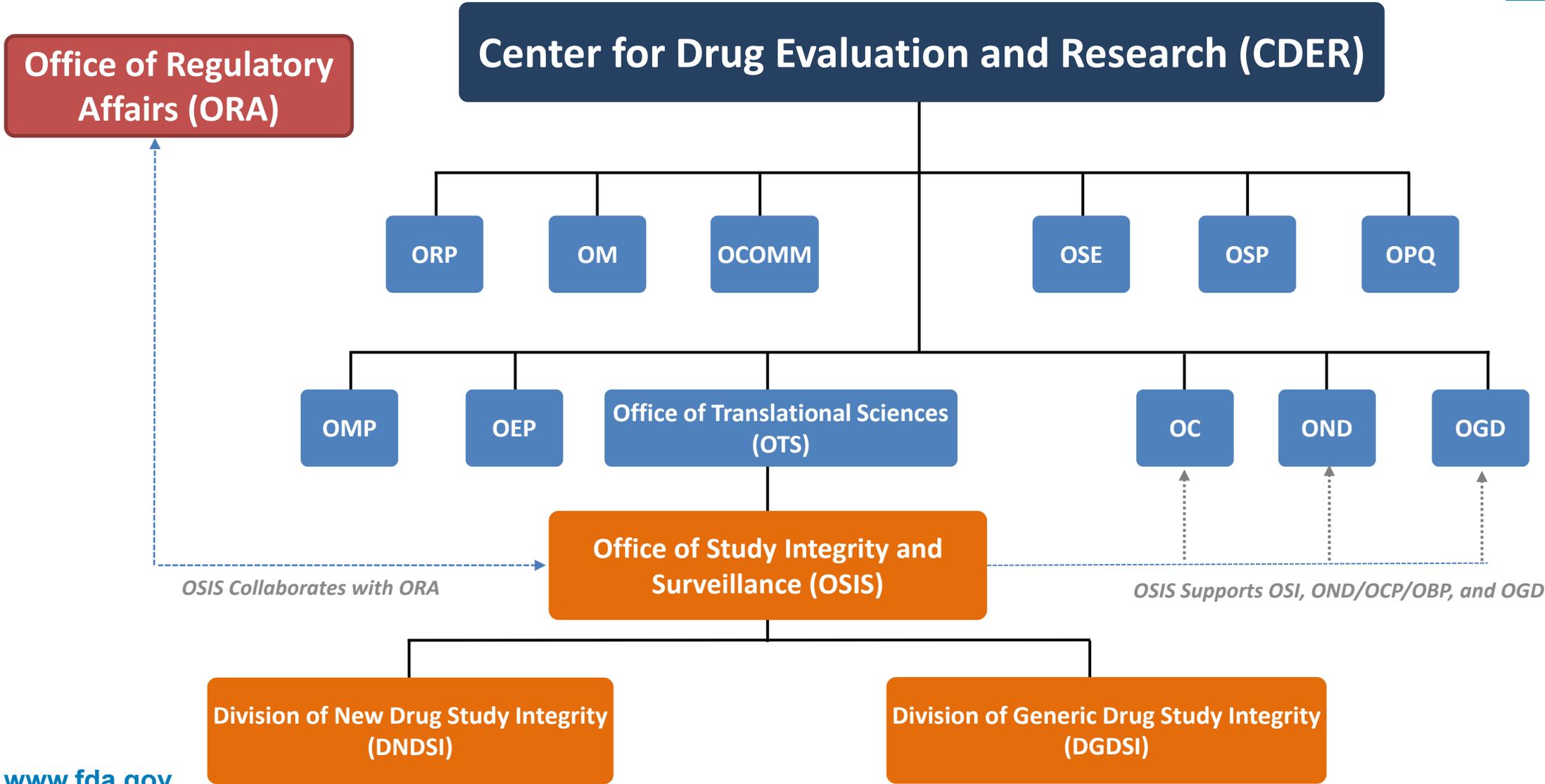
## OSIS Vision

- OSIS improves the public health by protecting study subjects and promoting properly conducted studies.

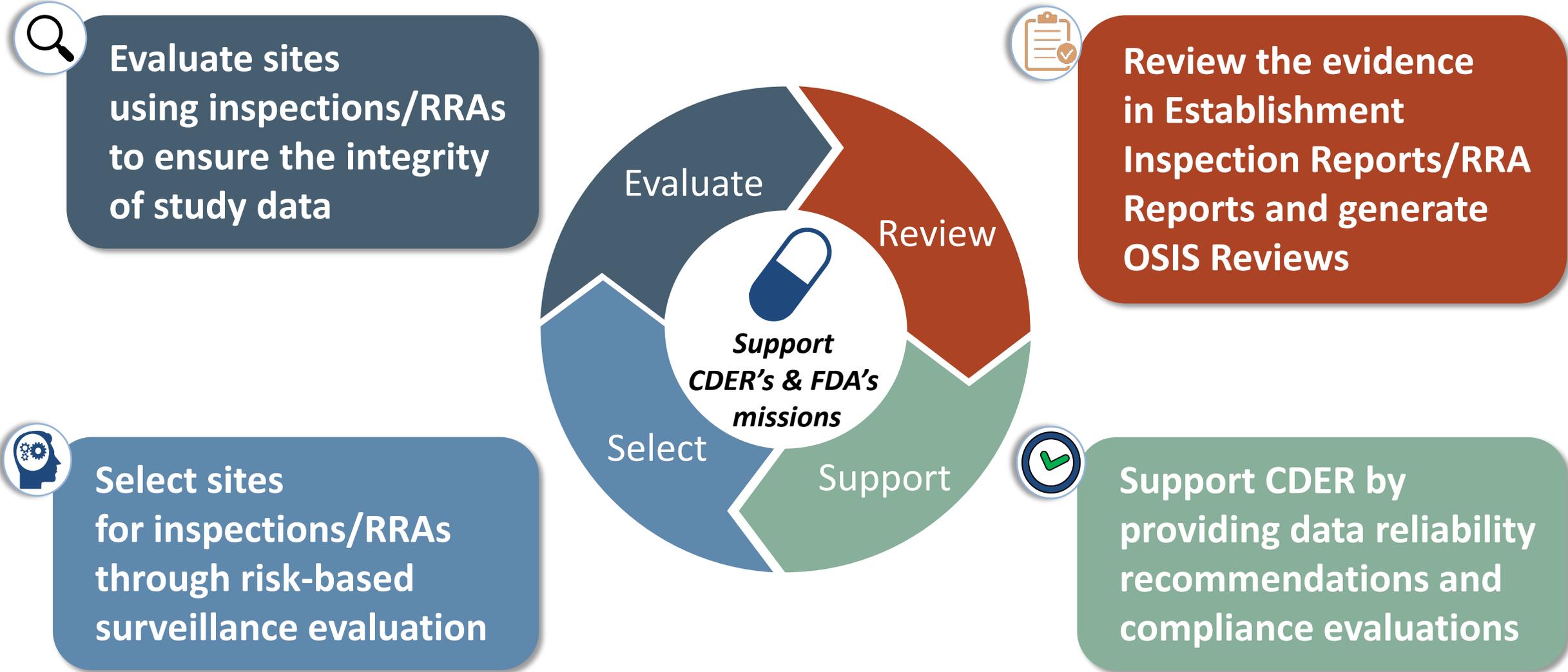
## OSIS Mission

- OSIS promotes the public health by ensuring the welfare of study subjects and by verifying the quality, study integrity and regulatory compliance of bioavailability/bioequivalence (BA/BE), nonclinical (GLP), and animal rule (AR) studies.

# Center for Drug Evaluation and Research



# OSIS Mission: **Select**, **Evaluate**, **Review**, **Support**



# BA/BE STUDY CONDUCT EXPECTATIONS

## Expectations for BA/BE studies

- Can the study be reconstructed?
  - Records need to support data before the Agency

## Absence of evidence is not evidence of absence

- Relevant or misapplied?
  - Study eligibility requires X, so what is expected?

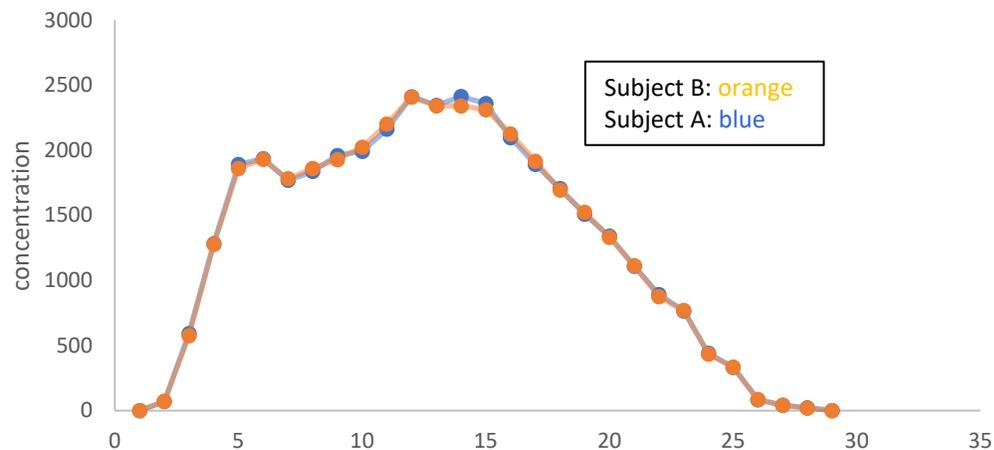
# DATA INTEGRITY

- Data are fundamental bases in the Agency's regulatory decision making
- Data integrity – the degree to which data are complete, consistent, accurate, and reliable
  - Data Integrity expected throughout lifecycle
    - Study design phase – what data controls needed?
    - During study – how is data integrity ensured?
      - Concurrent/contemporaneous and periodic review
- Data integrity is a shared responsibility

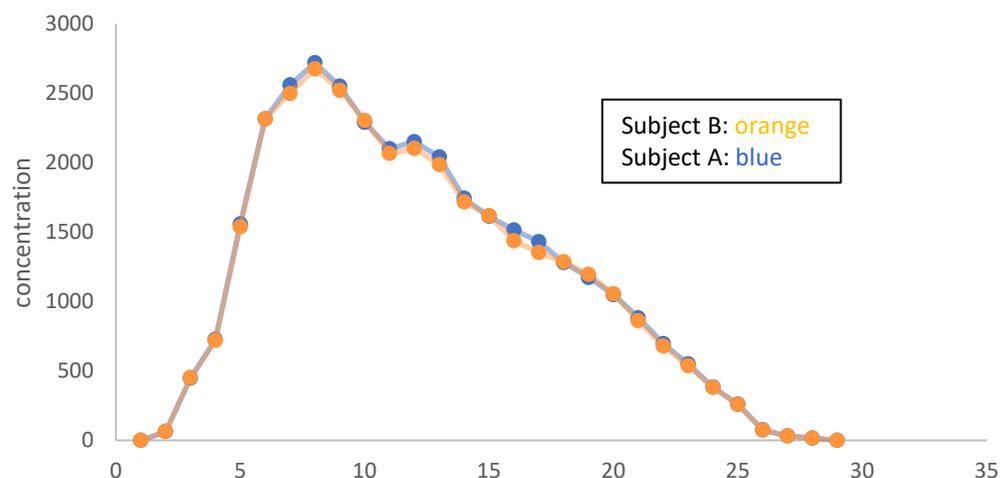
# DATA INTEGRITY – STUDY DIRE CASE EXAMPLE

- All site documentation reviewed: clinical and analytical
- Inspection: site provided the PK data sets and asked to plot the time-concentration profiles for multiple studies

Subject A P1 (T) v Subject B P2 (R)



Subject A P2 (R) v Subject B P1 (T)



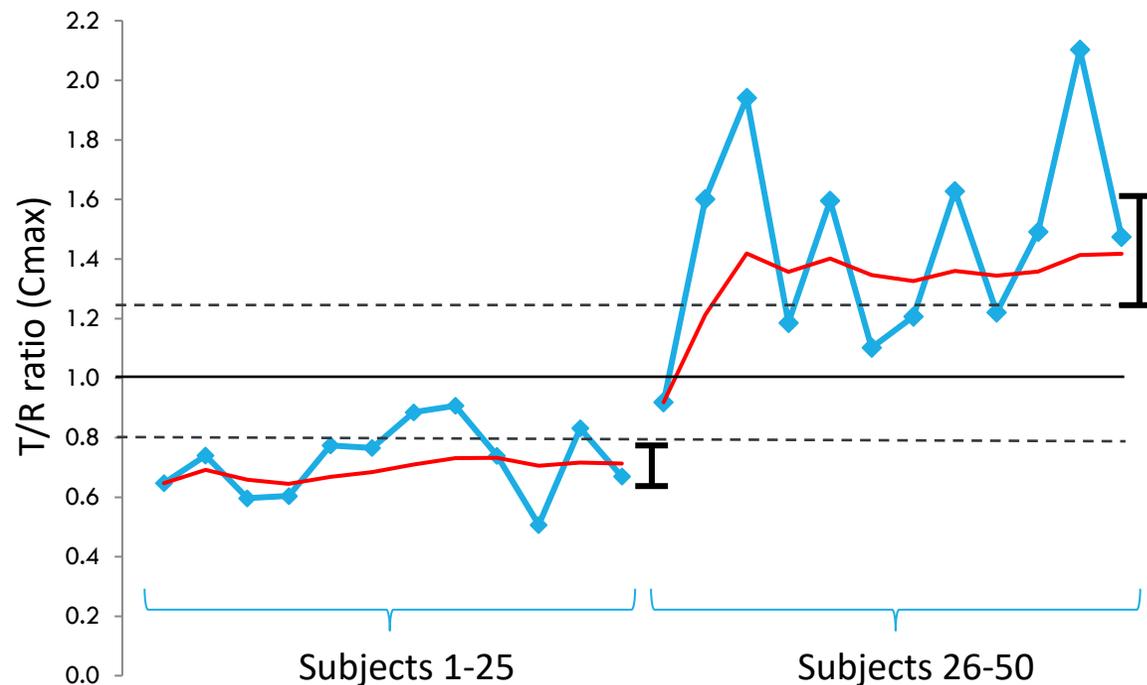
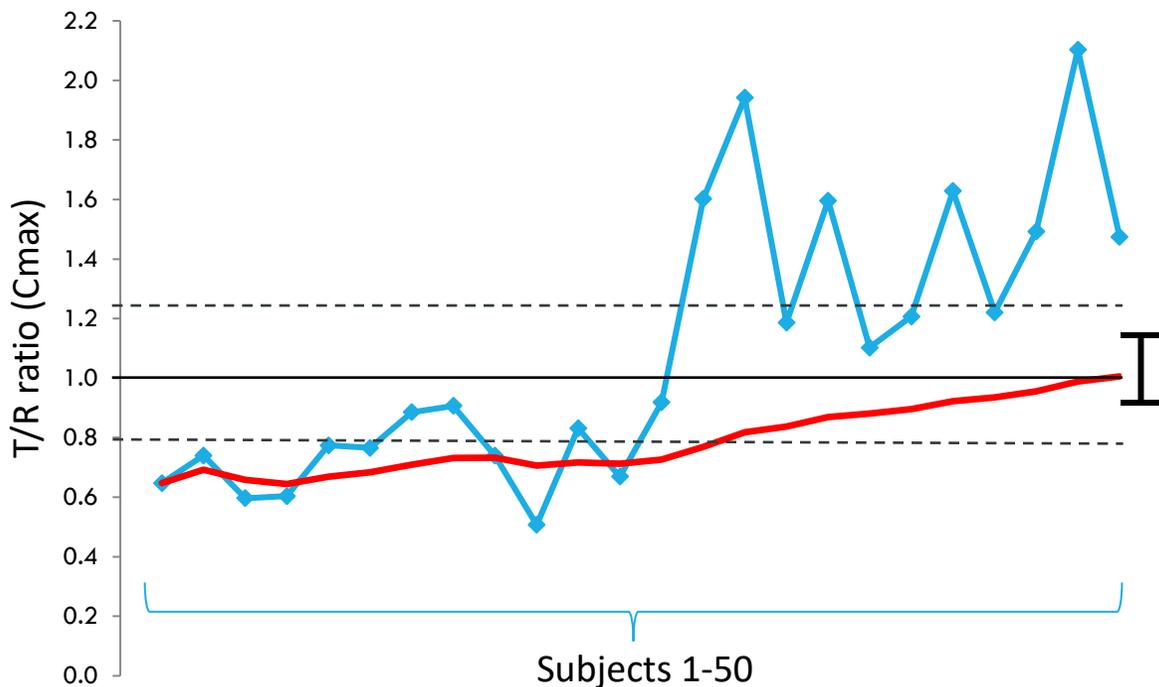
Study DIRE = Study Data Integrity and Reliability Example

# DIRE CASE EXAMPLE



## STUDY DIRE

- T/R Cmax
- Cumulative T/R Cmax
- 90% confidence interval



Study DIRE = Study Data Integrity and Reliability Example

## STUDY DIRE

- Testing Site provided FDA the following by subjects cohorts.

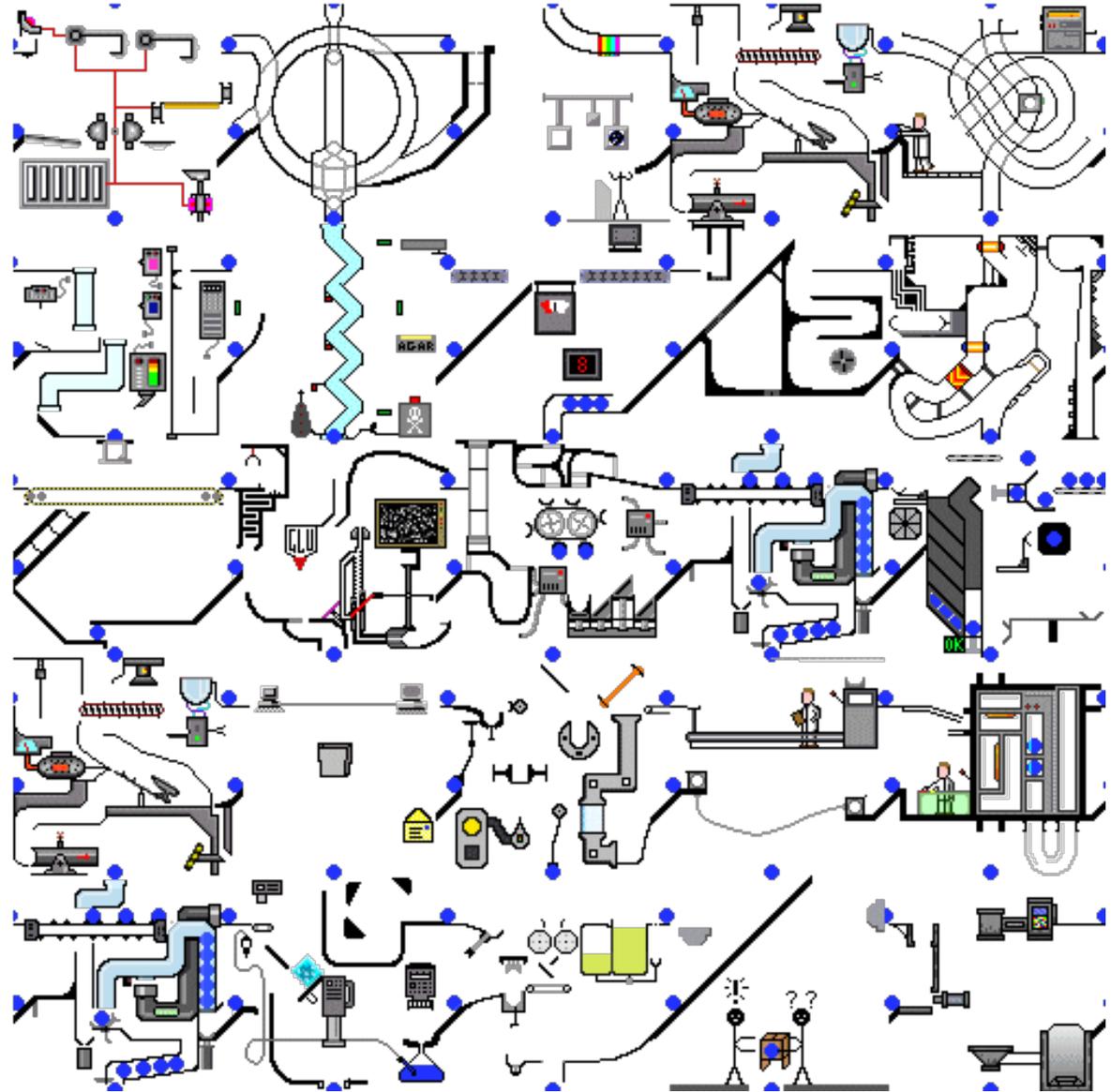
Study DIRE			
Subjects	Parameter	Point Estimate	90% CI
1-25 (n=25)	Cmax	71.26%	64.78 – 78.38
	AUC 0-t	85.41%	78.45 – 93.00
	AUC 0-inf	86.67%	79.98 – 93.91
16-50 (n=25)	Cmax	141.80%	124.27 – 161.82
	AUC 0-t	126.89%	115.81 – 139.04
	AUC 0-inf	124.52%	113.53 – 136.58
1-50 (n=50)	Cmax	100.52%	86.88 – 116.31
	AUC 0-t	104.11%	94.97 – 114.12
	AUC 0-inf	103.88%	95.28 – 113.26

# DATA INTEGRITY OUTCOMES

- Unexplainable anomalous data equates to data integrity issue undermining site's study conduct
- CDER determination, include:
  - Reliability of any studies and data generated from the site(s)
  - Impact on submissions to FDA: approved, tentatively approved, and pending
  - Need of BA/BE studies to be repeated at new site
- Significant discussions with foreign regulatory counterparts

# DATA INTEGRITY – BA/BE INTERNATIONAL COLLABORATION

IT'S  
COMPLICATED



# DATA INTEGRITY – BA/BE INTERNATIONAL COLLABORATION

- BA/BE studies environment results in significant international collaboration
  - Significant numbers of BA/BE studies conducted outside US (in whole or part)
  - Same products submitted for marketing authorization many countries
  - All Regulators have limited resources = collaboration is essential
- FDA and international regulators actions may differ
  - Similar study conduct expectations
  - Unique authorizing/legal frameworks

# CHALLENGE QUESTIONS

1. OSIS's BA/BE inspection program is focused on:
  - a. Verifying reliability and integrity of BA/BE study data submitted to FDA
  - b. Reviewing and approving submissions to FDA by verifying the reliability and integrity of BA/BE study data
  - c. Verifying the reliability, integrity and regulatory compliance of BA/BE studies submitted to FDA
  - d. None of the above

# CHALLENGE QUESTIONS

2. For comparable inspections (same site and same product), FDA BIMO inspection program actions will always mirror the regulatory actions of our foreign regulatory counterparts?
  - a. True
  - b. False



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