Data Reliability – BA/BE Inspections and Global Collaboration

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Disclaimer

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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

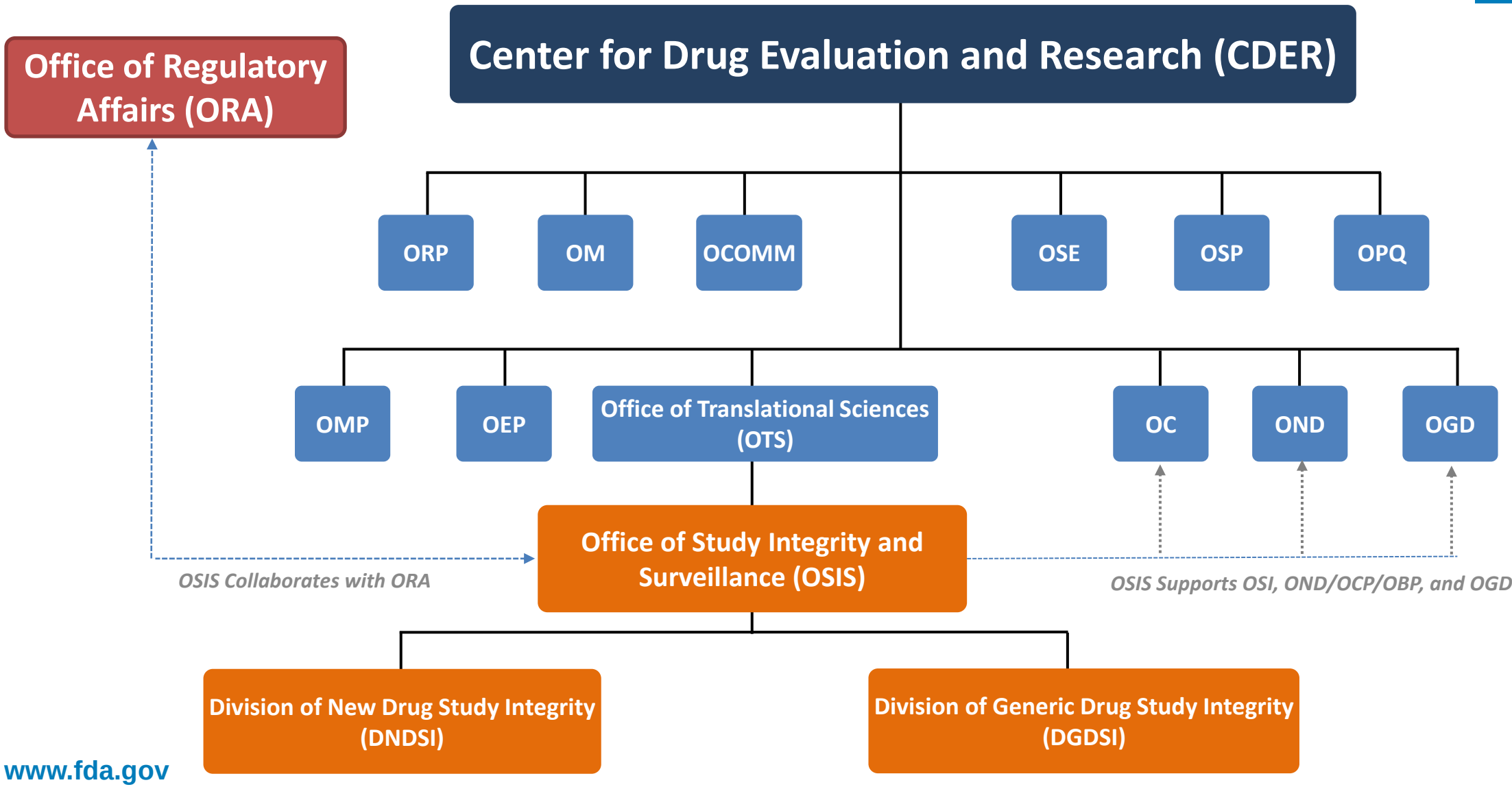
OSIS Vision

- 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.

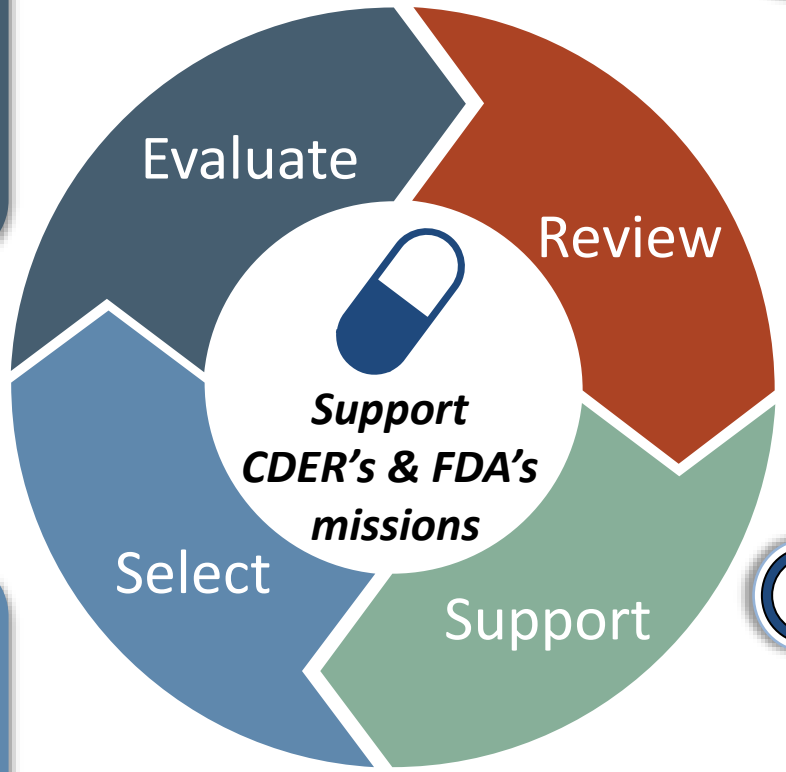
Center for Drug Evaluation and Research



OSIS Mission: Select, Evaluate, Review, Support

Evaluate sites using inspections/RRAs to ensure the integrity of study data

Review the evidence in Establishment Inspection Reports/RRA Reports and generate OSIS Reviews



Select sites for inspections/RRAs through risk-based surveillance evaluation

Support CDER by providing data reliability recommendations and compliance evaluations

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?

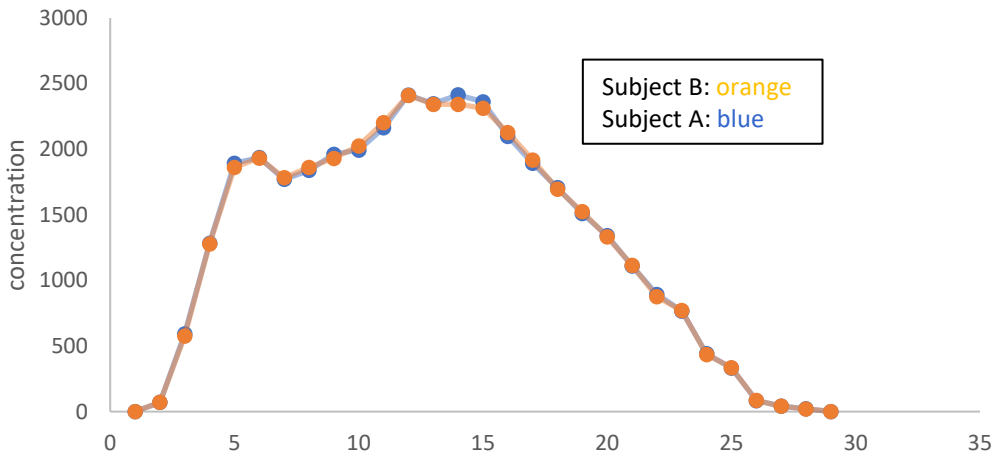
DATA INTEGRITY

- 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

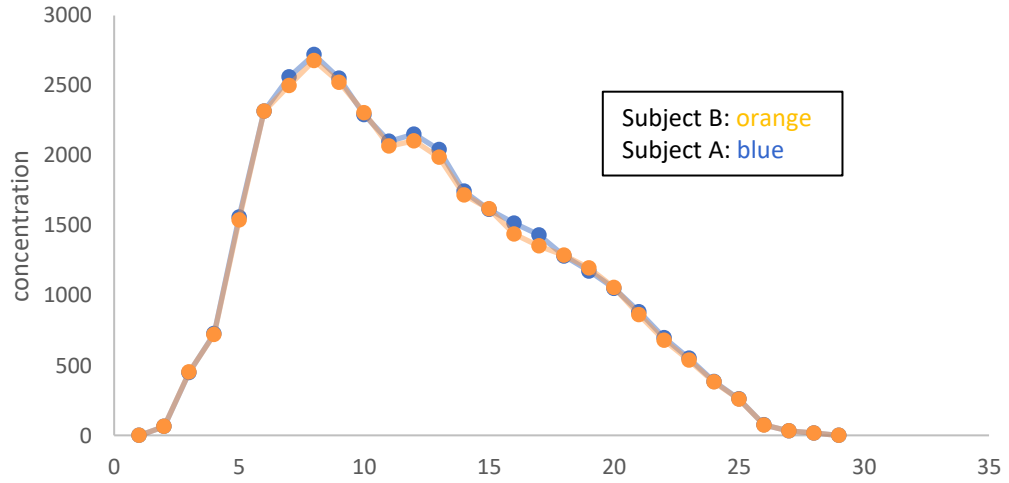
DATA INTEGRITY – STUDY DIRE CASE EXAMPLE

- 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)



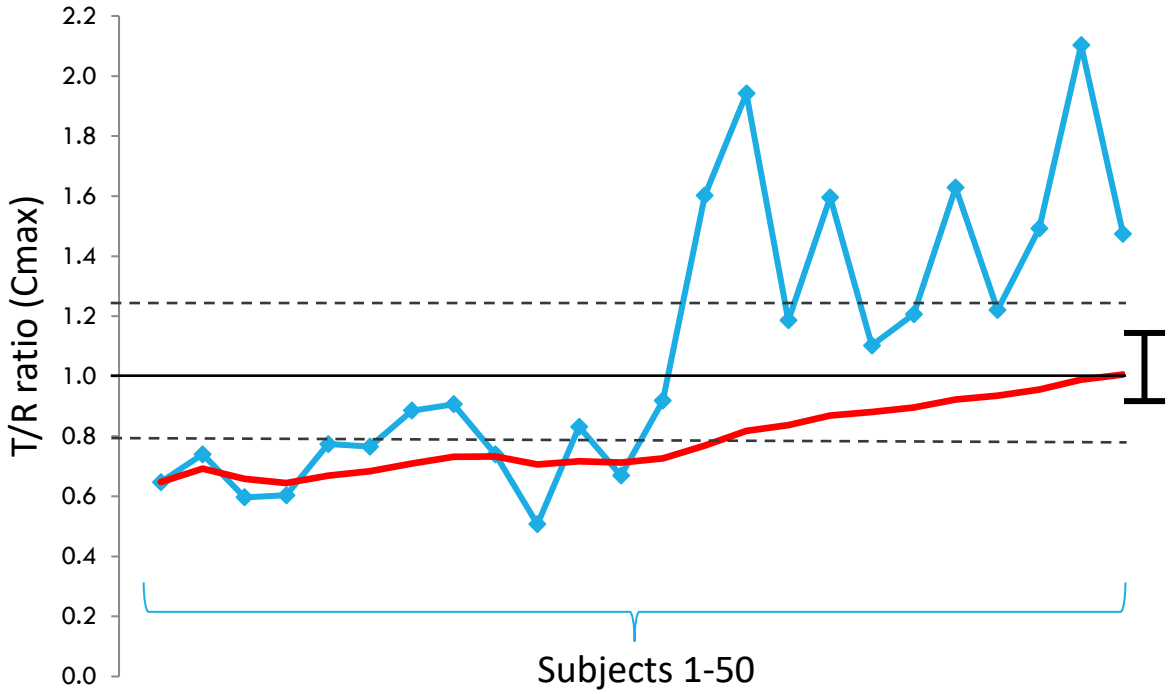
Subject A P2 (R) v Subject B P1 (T)

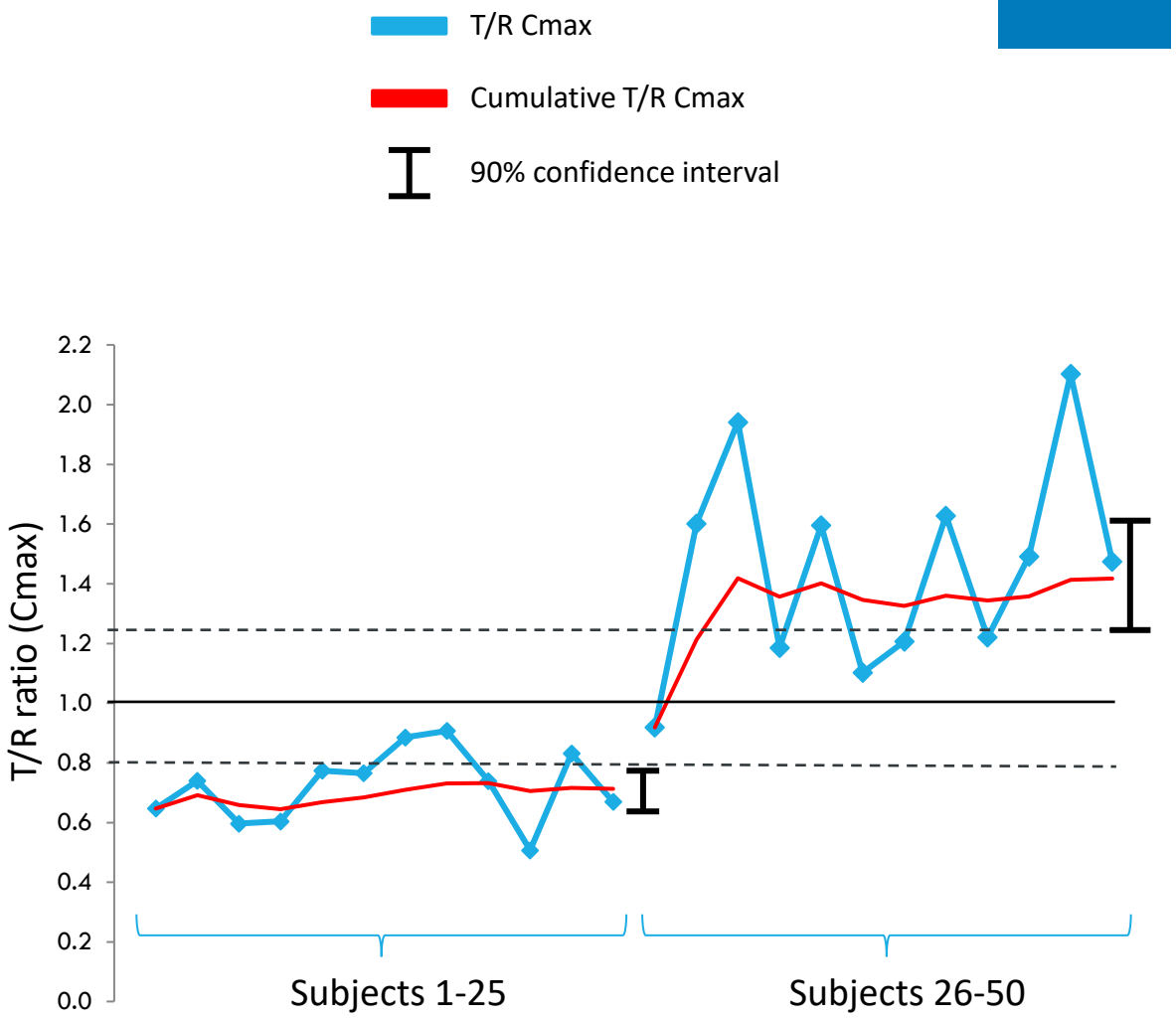


Study DIRE = Study Data Integrity and Reliability Example

DIRE CASE EXAMPLE

STUDY DIRE





Study DIRE = Study Data Integrity and Reliability Example

STUDY DIRE

- Testing Site provided FDA the following by subjects cohorts.

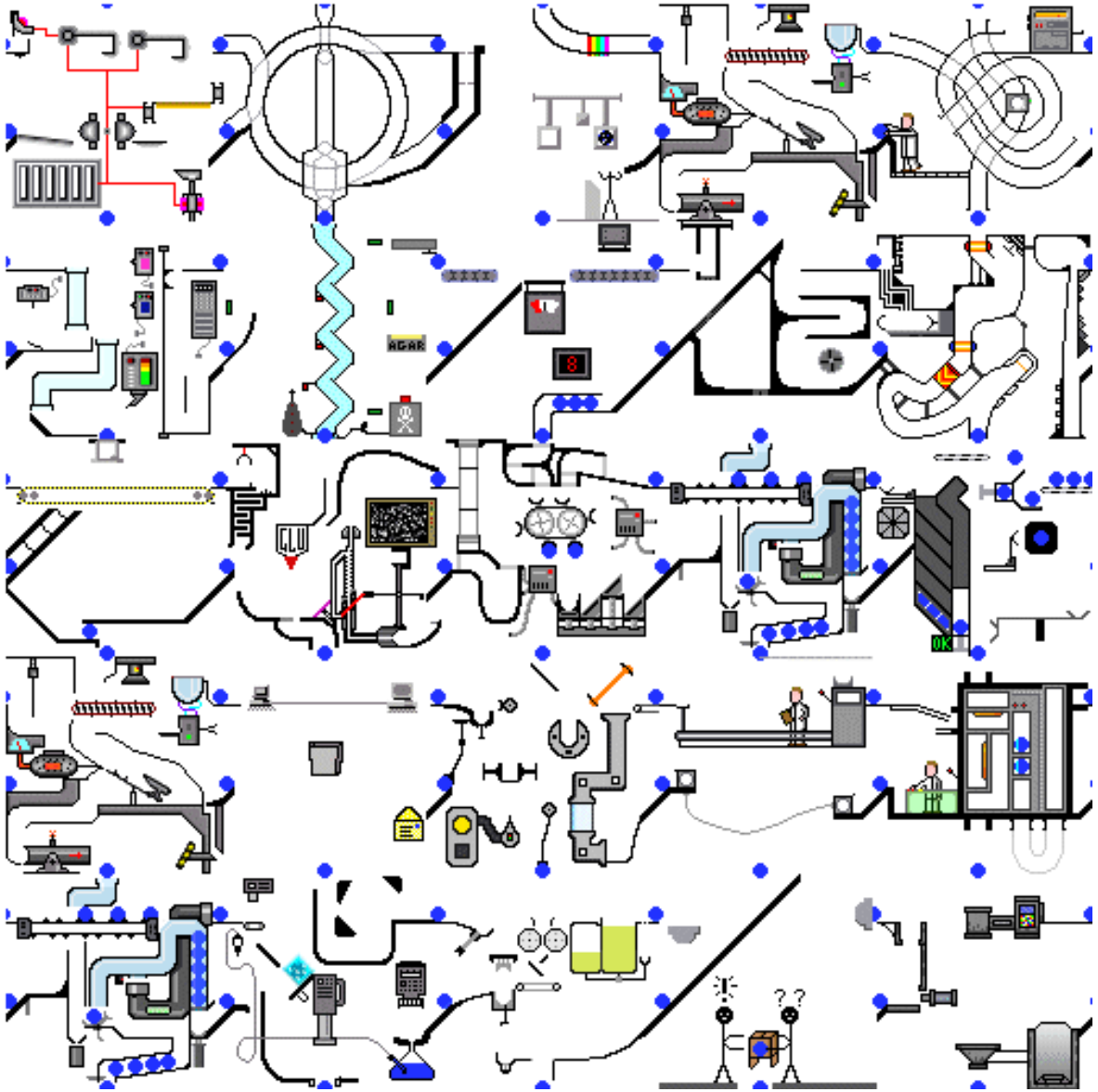
Study DIRE			
Subjects	**Parameter**	**Point Estimate**	**90% CI**
1-25 (n=25)	Cmax	71.26%	64.78 – 78.38
	AUC 0-t	85.41%	78.45 – 93.00
	AUC 0-inf	86.67%	79.98 – 93.91
16-50 (n=25)	Cmax	141.80%	124.27 – 161.82
	AUC 0-t	126.89%	115.81 – 139.04
	AUC 0-inf	124.52%	113.53 – 136.58
1-50 (n=50)	Cmax	100.52%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