Analytical Inspections for Bioavailability/Bioequivalence Studies

Li-Hong Yeh, Ph.D.
Chemist
Division of New Drug Study Integrity
Office of Study Integrity and Surveillance
OTS/CDER/FDA

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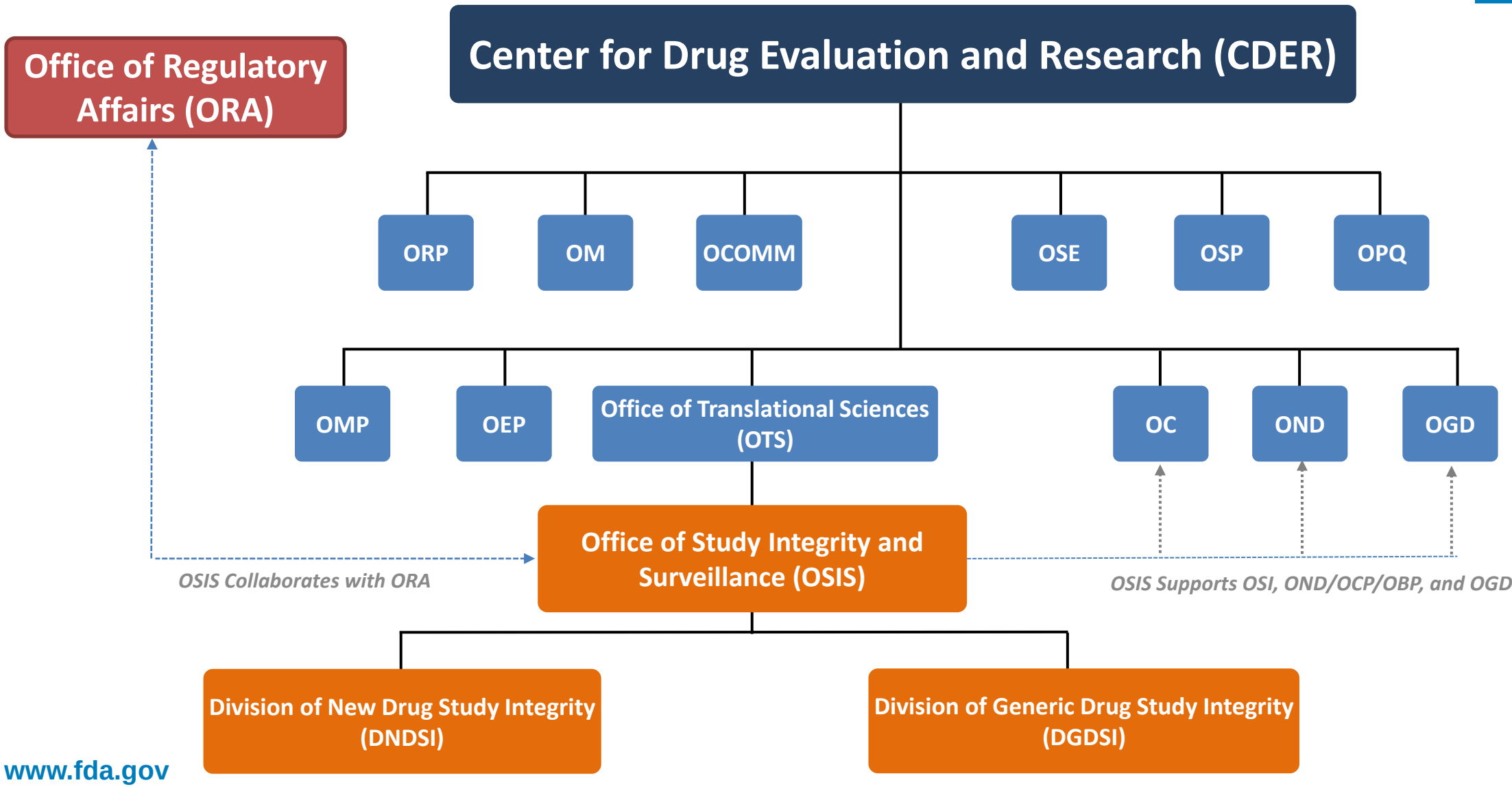
Learning Objectives

- Understand OSIS conduct of analytical inspections for bioavailability/ bioequivalence (BA/BE) studies
- Describe analytical inspections
  - On site inspection
  - Remote Regulatory Assessments (RRA)
- Common observations
- Closing remarks

FDA Bioresearch Monitoring (BIMO)

- Clinical investigators (CI)
- Sponsors / Contract Research Organizations (CRO)
- Institutional Review Board (IRB)
- Risk Evaluation and Mitigation Strategy (REMS)
- Post-market Adverse Drug Event (PADE)
- **Good Laboratory Practice (GLP) and Animal Rule (AR)**
- **Bioavailability/Bioequivalence (BA/BE)**

Where is OSIS?



BA/BE Bioresearch Monitoring (BIMO) Program

The objectives of the in vivo BA/BE Bioresearch Monitoring (BIMO) Program:

- To ensure the protection of the rights, safety, and welfare of human subjects participating in studies
- To ensure the quality, integrity and validity of clinical, analytical, and statistical data from BA/BE studies
- To ensure compliance with applicable FDA regulations and to identify significant deviations.

OSIS Assignment Workflow

- OSIS selects the sites for inspection
- OSIS sends inspection assignments to OSIS staff
- OSIS conducts analytical inspection
- OSIS prepare Establishment Inspection Report (EIR)
- OSIS review reports and exhibits and prepares OSIS Review Memo
- OSIS issues Closeout letter

Analytical Inspections

RRA Overview

- OSIS implemented a remote evaluation tool in June 2020
- Remote Regulatory Assessments (RRAs)
  - Draft Guidance for Industry on Conducting Remote Regulatory Assessments (July 2022)
  - https://www.fda.gov/media/160173/download
- RRAs allowed OSIS to continue to support the Generic, Biosimilar, and New Drug Review Programs through oversight of bioavailability, bioequivalence, GLP, and Animal Rule studies during the pandemic.

Inspectional focus and expectations*

1. Stability
2. Methodology
3. Documentation
4. Analysis of Study Samples

*Reference: M10 Bioanalytical Method Validation and Study Sample Analysis Guidance published in November 2022

Inspectional focus -(continued)

Analysis of Study Samples

- System suitability
- Run Acceptance
- Re-injection of study samples
- Internal standard variability (Trend)
- PK anomalies and re-assay
- Incurred sample reproducibility

Analysis of Study Samples

System Suitability (SS)

- Independent of study sample analysis
- Evaluated prior to analytical sample run
- Evaluated prior to resuming a sample analysis run after any instrument malfunction

Run Acceptance

- At least three QC levels in duplicate and LLOQ
- Runs meet acceptance criteria (75% CCs at 6 levels; at each level within 15% of nominal, 20% LLOQ) as mentioned in M10 Guidance

Analysis of Study Samples

Re-injection of Study Samples

- Justified, SOP driven, samples covered by validated processed sample stability
- All reinjected samples reported in study report

Internal Standard (IS) Variability/Drift

- SOP to determine run rejection based on variability or drift in IS response
- IS variability limits pre specified in SOP, QCs and samples with IS variability outside limit re analyzed

Analysis of Study Samples

PK Anomalies

- PK sample re-assay governed by SOP, potential reason investigated
- Sample repeat request documented with reason
- Anomalous and final concentrations reported with reason for selecting final concentration

Incurred Sample Reproducibility (ISR)

- Samples representing analyte Cmax and elimination half life
- Meet pre-defined acceptance criteria (67% samples values within 20% of original sample values)
- Procedures predefined for investigation of ISR failure

Inspectional focus -(continued)

Analysis of Study Samples

Does the documentation allow to reconstruct the study activities?

Common analytical observations

Analytical BA/BE

- Method not fully validated
- Inadequate stability data to cover sample storage and handling
- Incomplete documentation to allow reconstruction of study activities
- Rejection of analytical runs that met acceptance criteria
- Inconsistent run acceptance
- Data security – inappropriate access privileges

Summary

- OSIS supports FDA mission by ensuring data supporting regulatory decisions are reliable
- OSIS conducts on site inspection of analytical sites for surveillance purpose
- Remote regulatory assessment (RRA) is a tool that OSIS used during COVID-19 pandemic and will continue to use in assisting FDA in accomplishing its mission to protect public health
- Data submitted to FDA should be complete, accurate, and reliable to ensure safety, efficacy, and quality of drug products

Challenge Question #1

OSIS conducts analytical site evaluations to ensure data integrity by onsite inspections only. True or False?

A. True

B. False

C. Depends

Challenge Question #2

Which method OSIS uses to conduct BA/BE site evaluation:

1. On site inspection
2. Remote regulatory assessment
3. Both
4. None of the above


Thank
you!!


QUESTIONS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