Session 3 (BE): Clinical Study Conduct

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 15, 2024 – 11:00 – 11:40 AM

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Clinical Trial Study Conduct

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A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 13, 2024

Medicines & Healthcare products Regulatory Agency

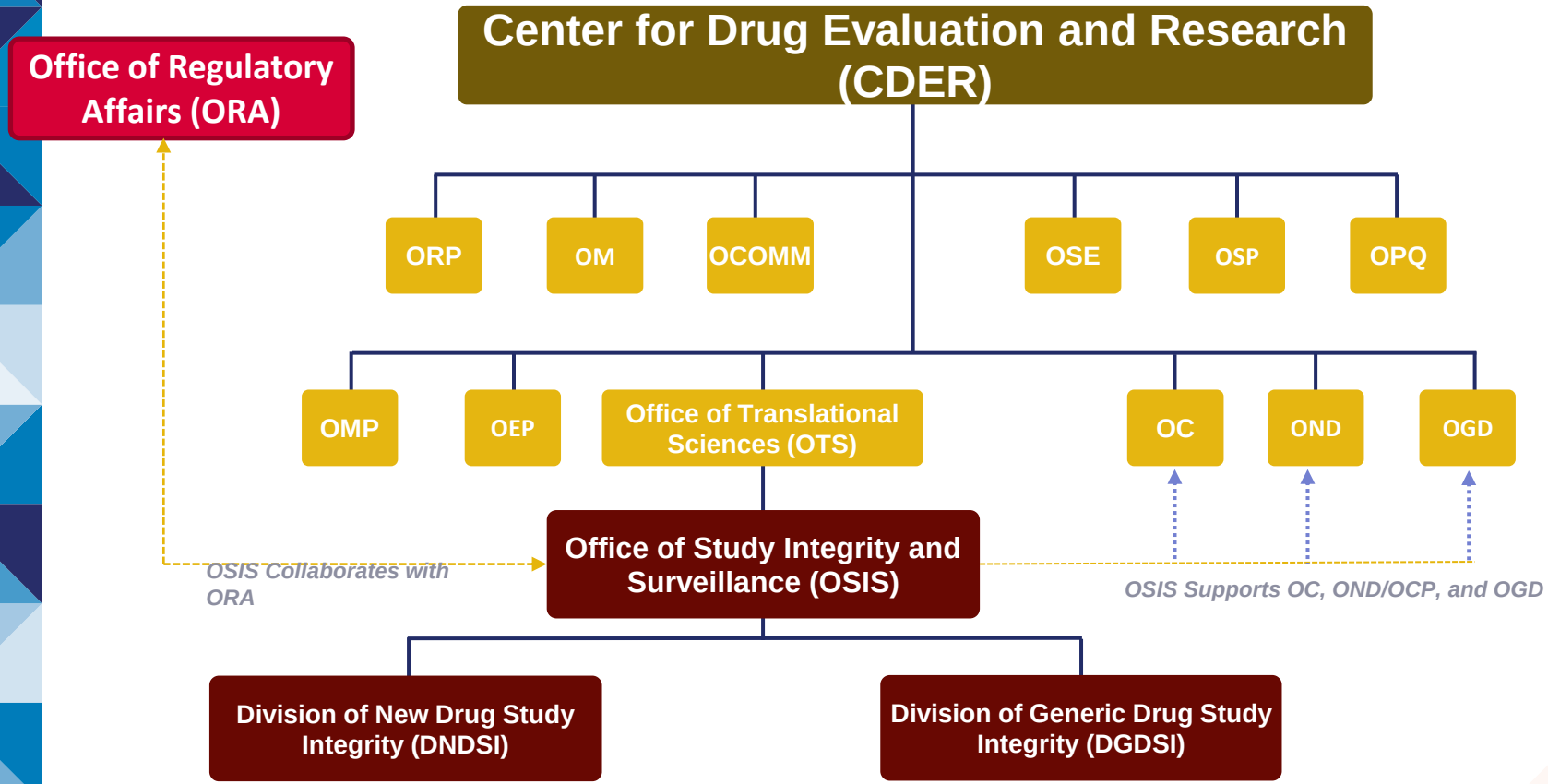
Health Canada Santé Canada

Disclaimer

The contents of this presentation are my own and do not necessarily reflect the views and/or policies of the Food and Drug Administration or its staff.

Learning Objectives

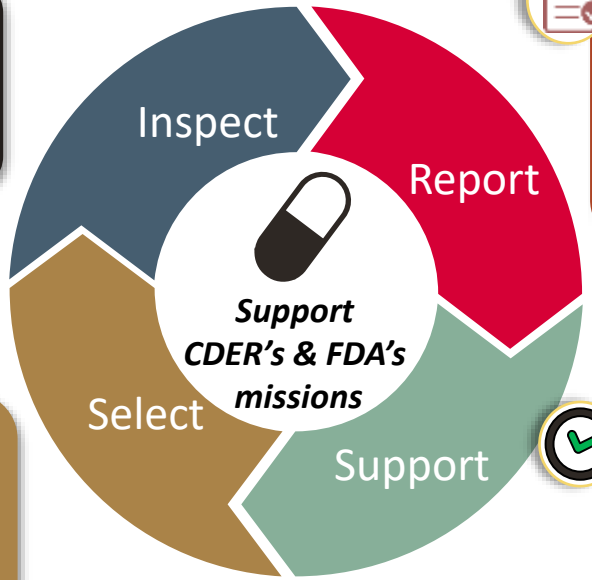
- Understand the FDA Bioresearch Monitoring (BIMO) Program
- Understand the source documentation requirements to determine subject eligibility and concerning trends
- Understand the content requirements of informed consent forms (ICF) and concerning trends


Center for Drug Evaluation and Research (CDER)
Office of Regulatory Affairs (ORA)
ORP
OM
OCOMM
OSE
OSP
OPQ
OMP
OEP
Office of Translational Sciences (OTS)
OC
OND
OGD
Office of Study Integrity and Surveillance (OSIS)
OSIS Collaborates with ORA
OSIS Supports OC, OND/OCP, and OGD
Division of New Drug Study Integrity (DNDSI)
Division of Generic Drug Study Integrity (DGDSI)

OSIS: Select, Inspect, Report, and Support

Inspect sites to ensure quality and integrity of studies

Select sites for inspection through surveillance evaluation and site assessment



Report on inspections by writing Establishment Inspection Reports and EIR Reviews

Support CDER with data reliability recommendations and compliance evaluations

FDA Bioresearch Monitoring (BIMO) Compliance Programs

- Provide instructions to FDA personnel for conducting compliance activities such as on-site inspections and data audits
- Compliance activities are used to:
  - Protect the rights, safety, and welfare of human research subjects
  - Verify the accuracy, reliability, and integrity of clinical and non-clinical trial submitted to FDA

Program #	Compliance Program Title
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies
7348.808	Good Laboratory Practice (Nonclinical Laboratories)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections
7348.809	Institutional Review Board
7348.809A	Radioactive Drug Research Committee
7348.810	Sponsors and Contract Research Organizations
7348.811	Clinical Investigators and Sponsor-Investigators
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections

BIMO Compliance Program 7348.003

In Vivo Bioavailability-Bioequivalence Studies - Clinical

CHAPTER 48 – BIORESEARCH MONITORING

SUBJECT:	IMPLEMENTATION DATE:
Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Clinical)	05/01/2018

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Product coding not required for biopharmaceutical establishments	48003A CLINICAL IN-VIVO BA/BE (ANDAS) 48003N CLINICAL IN-VIVO BA/BE (NDAS AND BLAS) 48003P CLINICAL PEPFAR ANDA BA/BE 48003Q CLINICAL IN-VIVO PEPFAR NDA BA/BE 48003B CLINICAL BA/BE - BIOSIMILARS

PART III – INSPECTIONAL

1. Organization
2. Study Administration and Responsibility
3. Subjects' Records and Documentation
   - A. Study Source Records
   - B. Informed Consents
   - C. Other Study Records
4. Test Article Accountability and Disposition
5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis
6. Randomization
7. Blinding Codes
8. Reserve Samples
9. Review of Electronic Data
10. International Inspections of Clinical BA/BE Study Sites
11. Reporting

BIMO Compliance Program 7348.003

3. Subject's Records and Documentation

A. Study Source Records

- Determine whether the study subjects met the eligibility criteria (inclusion/exclusion criteria)
- Compare the study source data at the clinical site with the background materials provided by the Center. If discrepancies are found, document them and review the case report forms for accuracy
- Determine whether adverse events (AEs) and the serious adverse events (SAEs) were accurately and adequately documented in the source records
- Describe the study source data files in terms of their organization, condition, accessibility, and completeness. For example, is the information on study source records attributable, legible, contemporaneous, original, and accurate (ALCOA)
- Determine whether there is adequate documentation that all study subjects were alive and actively participated during the study

Concerning Trends regarding Documentation and Subject Eligibility

- Concerning trend 1:
  - Lack of documentation to demonstrate subject eligibility
    - Example: For a clinical study, the source records for subject 12 showed that the subject met the inclusion criteria for prior use of a drug before enrollment as required by the protocol. However, there were no records indicating whether the subject had achieved a certain dose for a 2-week period prior to enrollment.

Concerning Trends regarding Documentation and Subject Eligibility

- Concerning trend 2:
  - Conflicting documentation that questions subject eligibility
    - Example: For a clinical study, subject 12 was required to have a grade of 3 Investigator Global Assessment of Acne (IGA) prior to enrollment per the study protocol. Source medical records indicate a grade of 3 on 06/21/18. However, source records from 07/01/18 indicate a grade of 1.

Concerning Trends regarding Documentation and Subject Eligibility

- Concerning trend 3:
  - Documentation is unreadable or lacks attribution to specific subject
    - Example: For a clinical study, the inspection uncovered a large collection of source medical records used to demonstrate subject eligibility at the clinical site. However, none of the records contained subject or patient identification where you can match records to enrolled subjects.

BIMO Compliance Program 7348.003

B. Informed Consent

- Did the subject's legal-authorized representative sign the informed consent document prior to entry into the study (e.g., prior to performance of any study related tests, and administration of the test article)? If the subject did not sign the informed consent document, determine who signed it and that person's relationship to the subject.

- Determine whether the consent document(s) complies with the elements of 21 CFR 50.25, 21 CFR 50.56, and ICH E6, and document any discrepancies or concerns.

Part 50: Protection of Human Subjects

50.25 Elements of informed consent:

a) Basic elements of informed consent

1) Statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

Concerning Trends of Informed Consents

- Concerning trend 1:
  - ICF contains language that seems to imply that the clinical study is not experimental:
    - Example: For a specific clinical study, the informed consent form used to enroll subjects included the following statement:

"This study is a clinical research project, but no part of it is of an experimental nature…"

Concerning Trends of Informed Consents

- Concerning trend 2:
  - ICF contains language that seems to downplay risks associated with clinical study:
    - Example: For a specific clinical study, the informed consent form used to enroll subjects included the following statement:

"The [insert drug name] has been on the market for quite some years and all aspects of its usage are well studied, there are no unforeseeable risks associated with it."

Questions?

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MHRA Bioequivalence Inspections - Clinical

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MHRA bioequivalence (BE) inspections

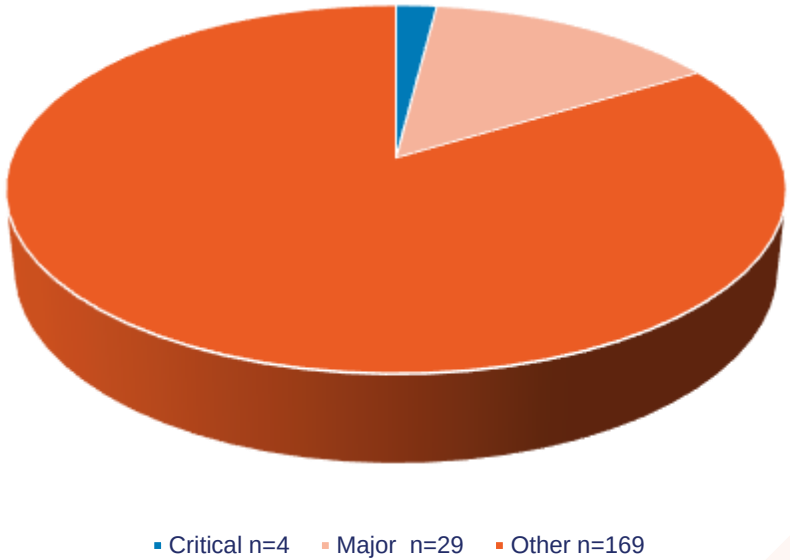
24 inspections performed since 2019

Remote (office-based) inspections between October 2020 and June 2022

Combination of inspections approaches since June 2022:

- Remote
- On-Site
- Hybrid

Distribution of findings 2019 - 2023



Critical Findings (n=4)

Subject eligibility**

Clinical sample analysis**

Method validation**

Data integrity**

***Ineligible subjects recruited into studies*

***Related to clinical sample analysis*

Major Findings (n=29)

CRF/source data (n=3)

Subject eligibility (n=2)

IMP management (n=2)

Quality assurance

Subject safety

Facilities and equipment

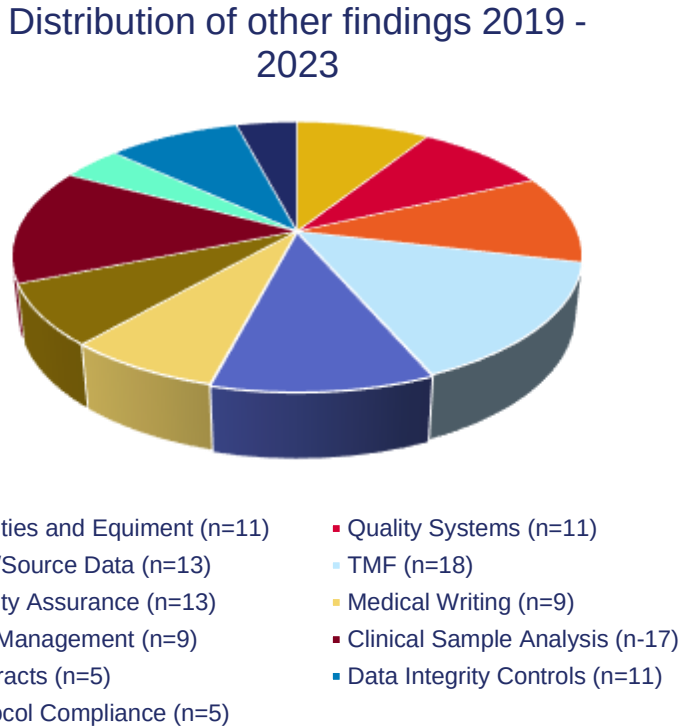
Archiving

Medical oversight

Method validation (n=4)
Data integrity controls (n=4)
Clinical sample analysis (n=5)

Quality systems
Competent Authority
Reporting
Data management

Other findings (n=169)



Also…..

- Subject safety
- Medical oversight
- Computerised systems
- Competent Authority
- Project management
- Written informed consent
- Insurance
- Training
- Management of medical emergencies
- Research Ethics Committee
- Staff delegation and responsibilities
- Computer systems validation
- Subject confidentiality
- Statistics
- Monitoring
- Sample management
- Method validation
- Reporting
- Subject eligibility
- Protocol compliance

MHRA common findings

- Clinical pathology laboratories
- IMP management
- Computerised systems:
  - Electronic case report forms (eCRF)
  - Volunteer databases

- Facilities and equipment
- Electronic archiving
- Insurance
- Transparency

Clinical pathology laboratories (1)

Vendor assessment

Multiple laboratories in one study with different reference ranges

Discrepancies between in house and laboratory reference ranges

Sufficient stability for laboratory testing?

Clinical pathology laboratories (2)

Clinical significance:

- Missed assessments – still common
- Assessments done but not permitted by the protocol

Additional testing in the laboratory not required as per protocol

Eligibility issues

IMP management

Certificates of analysis

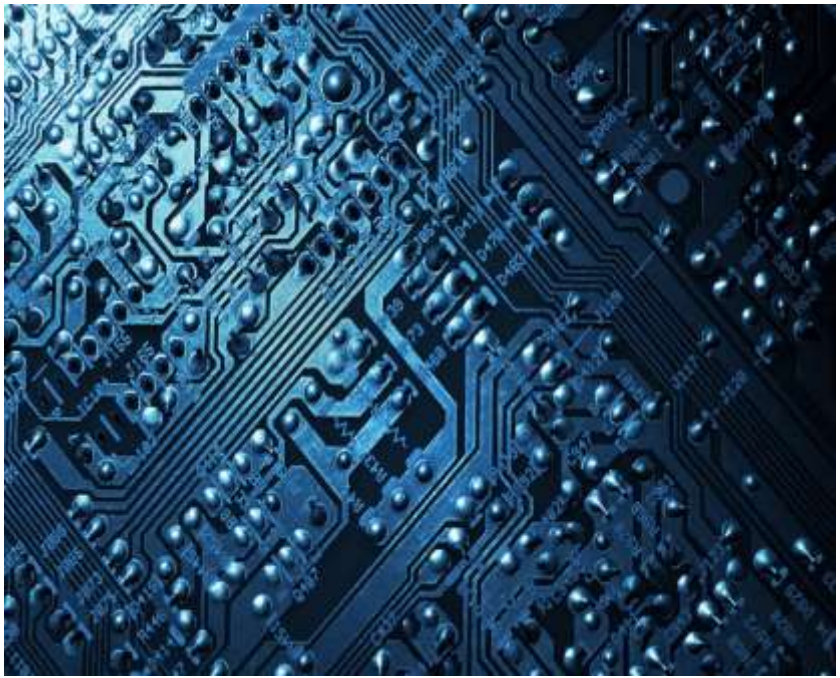
- Expiry dates
- Out of specification results
- Missing data
- Provisional data

IMP verification checks

Data loggers

Novel product formulations

Computerised systems (1)



Electronic case report forms (eCRF)

Insufficient audit trails
- No functionality
- Limited functionality

No capacity for study specific builds

Barcoding

System development in ‘live’ environment

Computerised systems (2)

Volunteer databases

Data migrations
- Incomplete
- Poor documentation

Biometrics
- Incorrect identification
- Lack of specificity

Facilities and equipment

Washrooms

Alarm points

Equipment maintenance and calibration:

- ECGs
- Testing kits
- Automated interfaces with eCRF/volunteer database

Electronic archiving

Metadata not archived

- Digital ECGs
- Volunteer databases
- Digital X rays
- eCRF
- Electronic clinical pathology laboratory reports

Insurance

Lapses in cover

Exclusions:

- Specific populations
- Specific regions
- Specific medicines
- Specific studies

Transparency (1)

Could apply to any study documentation and/or activity.

Ask yourselves:

- I know what I mean but is that what it says?
- Do any assumptions need to be made regarding what has been written?
- Could this be misinterpreted?

Transparency (2)

Example 1:

Not all QA process audits had been included on QA statements in study reports and there were no qualifying statements to indicate that additional audits had been performed.

Objective reviewer would not be aware that additional audit activity had been conducted which may help support/further support study conduct

Transparency (3)

Example 2:

Paper records indicated that study procedures were ‘ND’ indicating ‘not done’ with extra associated coding ‘X’ which related to ‘subject non-compliance’.

This suggested that subjects had been non-compliant when, in practice, a study procedure had not been performed by staff.

Transparency (4)

Example 3:

The final participant had been excluded from the study for ‘other’ reasons

Sufficient study data available for a statistically powered dataset without including the final participant

Transparency (5)

Example 4:

Two subjects were shown as ‘not dosed’ in IMP data but dosing data and subsequent clinical data was available in CRFs for both.

Too long had passed between dispensing and dosing on a specific date (protocol restriction) and subjects were dosed on a later date.

Reminder…

Ask yourselves:

- I know what I mean but is that what it says?
- Do any assumptions need to be made regarding what has been written?
- Could this be misinterpreted?