Session 1 (BE): Remote Evaluations

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 15, 2024 – 9:00 – 9:40 AM

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Remote Regulatory Assessments (RRAs) - A Valuable Tool for OSIS to support Drug Application Review in FDA

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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

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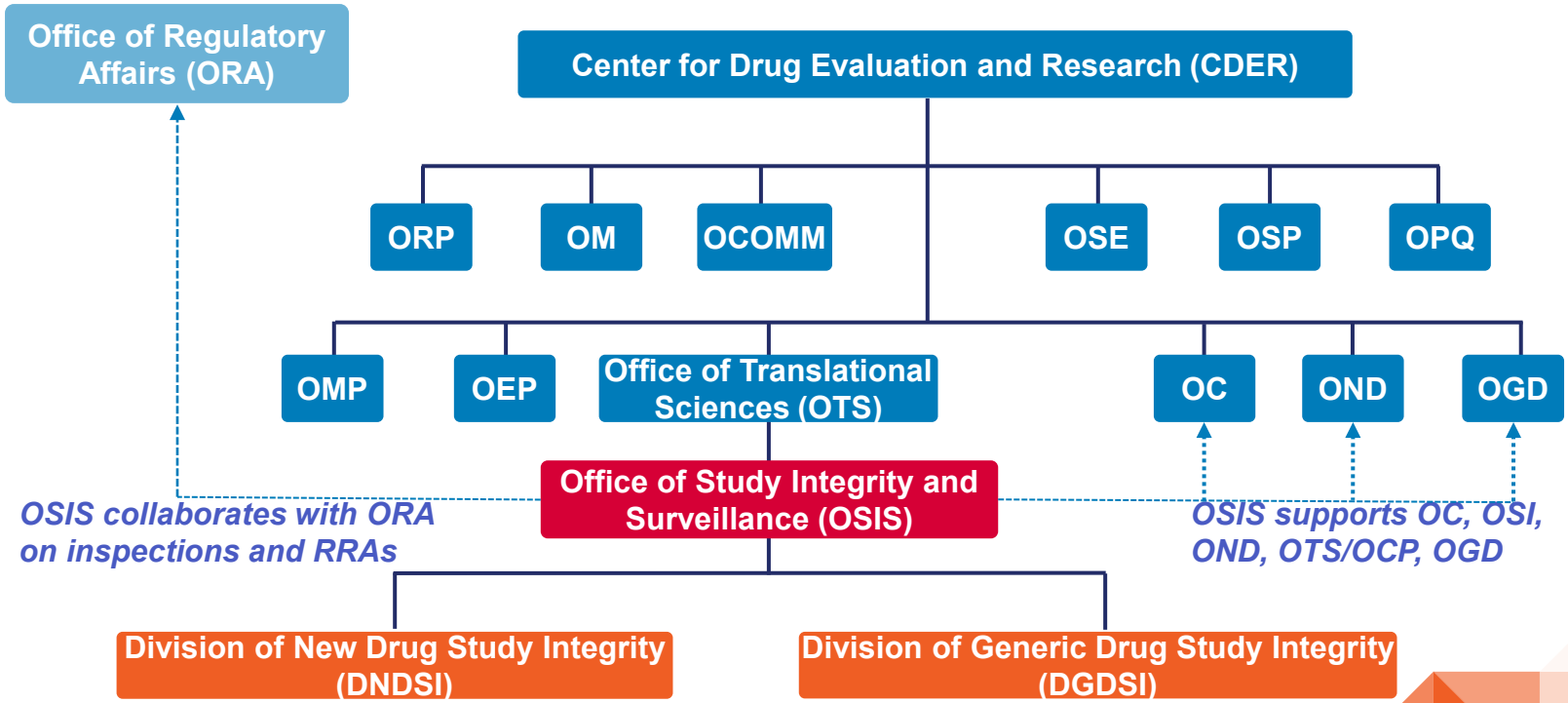
Overview

- Office of Study Integrity and Surveillance (OSIS)
- OSIS Oversee In Vivo Bioavailability/Bioequivalence (BA/BE) Studies
- Remote Regulatory Assessments (RRAs)
- Looking Forward

Office of Study Integrity and Surveillance (OSIS)



Office of Study Integrity and Surveillance (OSIS)

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.

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 (EIRs)/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

Typical In Vivo BA/BE Studies

Clinical component

- Clinical RRAs/inspections are mainly conducted by FDA/ORA staff and FDA/OSIS staff when needed.
- The clinical component involves the adequacy of the site, facilities, personnel, procedures, subjects screening, enrollment, investigational drugs administration, subject safety monitoring, protocol adherence, biological samples collection, and so on.

Typical In Vivo BA/BE Studies (cont'd)

Analytical component

- Analytical RRAs/inspections are mainly conducted by FDA/OSIS staff and FDA/ORA staff when needed.
- The analytical component involves the adequacy of site, facilities, equipment, personnel, biological samples processing, method validation, study sample analysis, documentation, data securing and reporting, and so on.

- **OSIS oversees in vivo BA/BE studies conduct at both clinical and analytical components**

Remote Regulatory Assessments (RRAs)

OSIS implemented RRA, a remote evaluation tool, in June 2020

- Draft Guidance for Industry on Conducting Remote Regulatory Assessments (July 2022) Conducting Remote Regulatory Assessments Questions and Answers | FDA
- Voluntary participation
- Requests records and other information prior to virtual interactions
- Issue written observations at close-out
- Provide data reliability/subject safety recommendations to review divisions

RRAs (cont'd)

- RRA allowed OSIS to continue to oversee the conduct of BA/BE, GLP, and AR studies during and beyond the pandemic, supporting the CDER review of NDAs, ANDAs, BLAs, and INDs, and meeting FDA's mission to protect public health.

RRA vs. Inspection

RRA Process

RRA Request and Preparation	Send communication letter seeking voluntary participation. RRA preparation includes the review of general information and study specific documents
Document Request and Review	Request documents through BOX.com FDA cloud filesharing solution
RRA Opening	Schedule and conduct an opening meeting via ZoomGov
Virtual Facility Tour	Review key operational areas, including instruments, sample receipt/storage areas, laboratories, archives, server room, etc.
Daily Meeting	Meet with site staff and management and discuss questions or concerns on data and/or study conduct
Close-Out Meeting	Hold a close-out meeting and issue written observations, as applicable. **No** Form FDA 483.

Inspection Process

Inspection Preparation	Inspection preparation includes the review of general information and study specific documents
Inspection Opening	In person. Present credentials and Form FDA 482 for domestic Opening on site. Document request
Facility Tour	Review key operational areas, including instruments, sample receipt/storage areas, laboratories, archives, server room, etc.
Daily Meeting	Meet with site staff and management and discuss questions or concerns on data and/or study conduct
Close-Out Meeting	Hold a close-out meeting and issue Form FDA 483 as applicable

Studies that OSIS conduct RRAs and inspections to support FDA's review of NDAs, BLAs and ANDAs

- In Vivo Bioavailability/Bioequivalence/Pharmacokinetics/Ligand Binding Assay (BA/BE/PK/LBA) Studies
- In Vitro BE Studies
  - In Vitro Permeability Testing (IVPT), In Vitro Release Testing (IVRT), In Vitro Particle Size Distribution (PSD) Study, In Vitro Globule Size Distribution (GSD) Study, In Vitro Liposome Size Distribution Study, In Vitro Dissolution Testing for BE Determination, In Vitro Equilibrium Binding Study, In Vitro Kinetic Binding Study, and so on.
- To support regulatory decisions regarding drug application safety, efficacy and labeling

Case Study 1 - a pivotal in vitro BE study to support an ANDA

During RRA, OSIS had one objectionable condition that the site did not store reserve samples for the reference drug product in an area segregated from the area where in vitro BE testing was conducted, per the 21 CFR 320.38/320.63 (retention of BA/BE samples).

- Specially, reserve samples for the reference drug product were stored in the refrigerator located in the analytical laboratory where the in vitro BE study was conducted.

Case Study 1 (cont'd)

- Evidence collected during the RRA confirmed that the site did not meet the regulatory requirement of 21 CFR 320.38/320.63.
- However, based on review of the drug product receipt and all relevant study records, OSIS was able to establish a complete accountability and the tracking/movement of the reference drug products that the site received, used, and retained.
- OSIS concluded that the data are reliable.

Case Study 2 – a pivotal in vivo PK study to support a BLA

- During RRA, OSIS found a discrepancy of concentration values of 36 samples (~1% data), which were documented as > LLOQ in source data but reported as < LLOQ in the submission.
- The data discrepancies were alerted to the CDER review division.
- FDA requested the Applicant for a clarification and found the explanation acceptable.

Looking Forward

- OSIS continues to improve and refine RRA for its remote process and effectiveness.
- RRA is a critical and valuable tool that OSIS will continue to use to assist FDA in accomplishing its mission of ensuring public health and safety.
- Data submitted to FDA should be complete, accurate, and reliable to ensure safety, efficacy, and quality of drug products.

Questions?

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An overview of remote and hybrid Bioequivalence Inspections conducted by the UK MHRA

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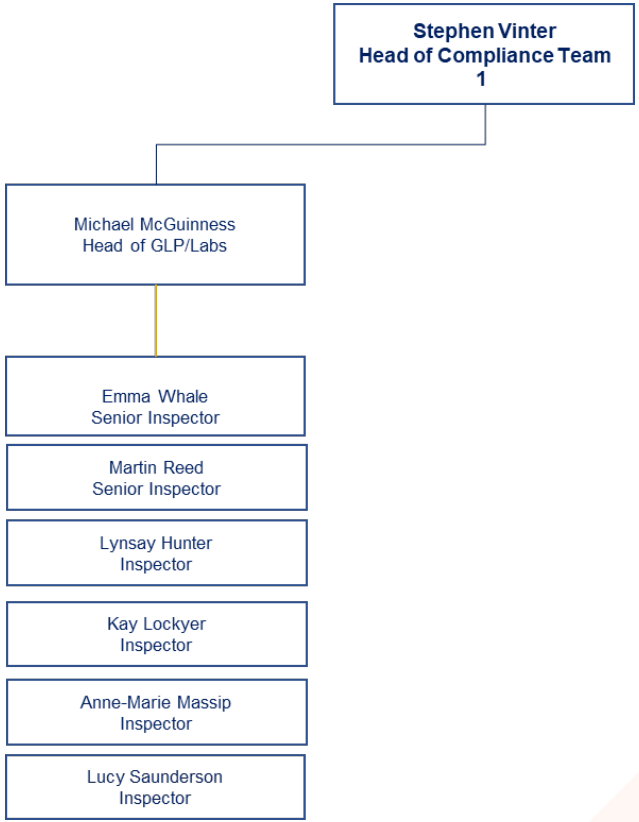
Overview

- MHRA Bioequivalence Inspections Overview
- Inspection Types
  - Onsite
  - Remote
  - Hybrid
- When will the different types be used?
- Feedback from Hybrid and Remote inspections

MHRA Bioequivalence Inspections Overview (1)

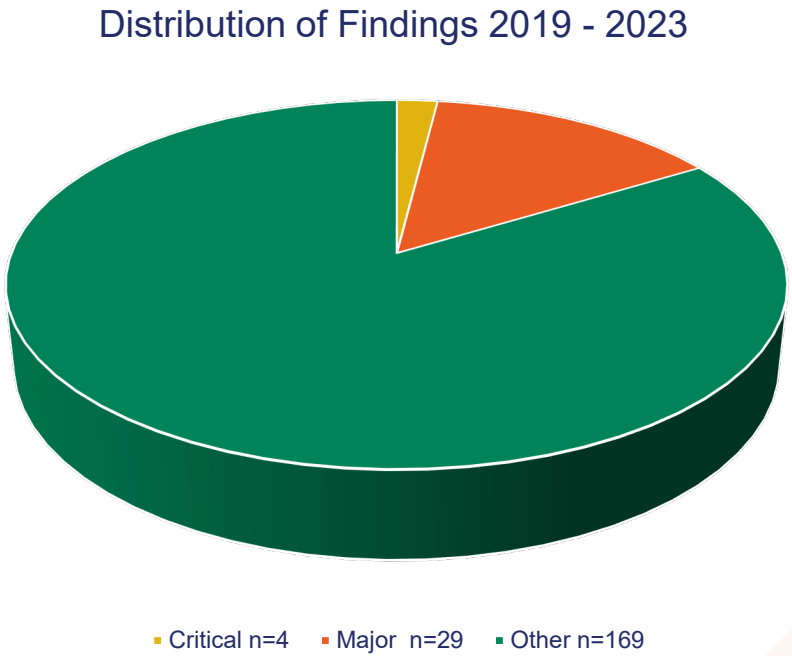
- BE Inspections are performed by the Laboratories Inspection Team.
- This is a multi-GxP team.
- Support can be provided by other Inspection Teams



MHRA Bioequivalence (BE) Inspections Overview (2)

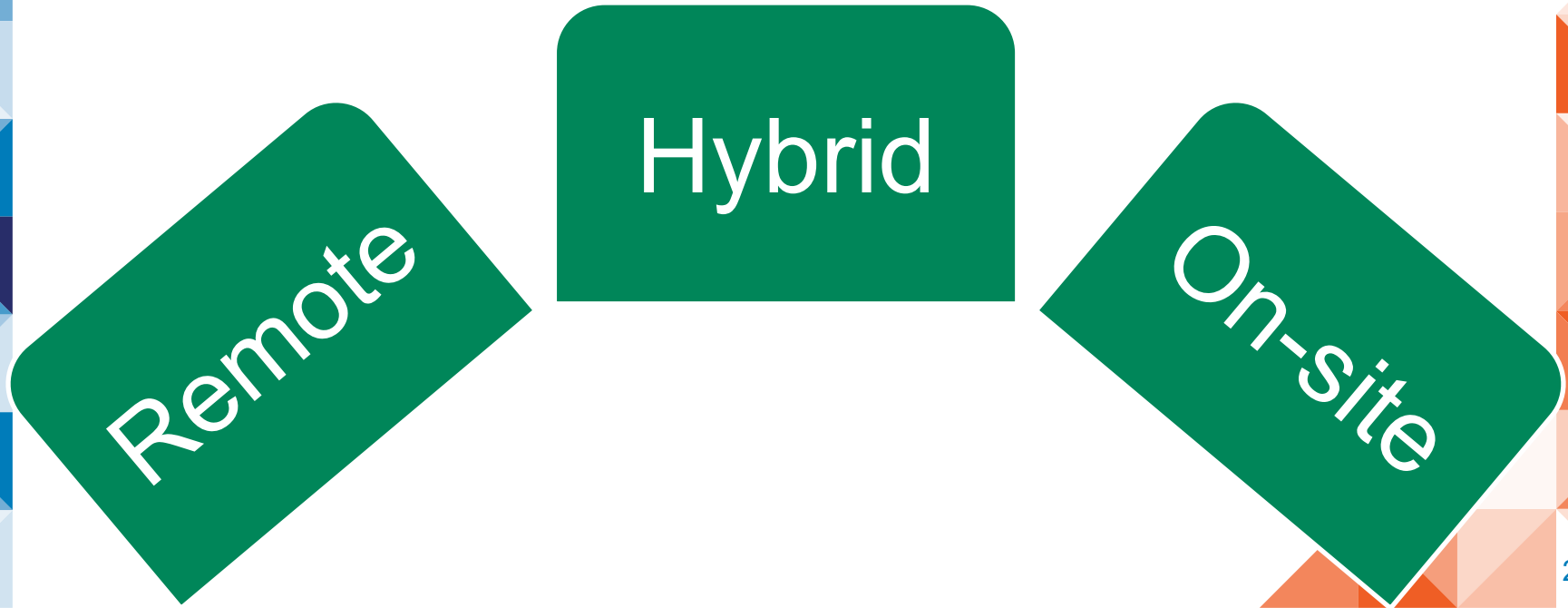
24 inspections performed since 2019

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



Inspection Types (1)

Combination of inspections approaches since June 2022



Inspection Types (2)

Notification & Data Requests → Inspection → Report & Closure

On-site Inspection

- All activity performed on inspection site.
- Sites will be asked to provide analytical in advance of the inspection.
- MHRA held analytical software (where possible) will be used for review of analytical data.

Remote Inspection

- All activity performed remotely.
- Use of visual technology to facilitate walkthroughs using MS Teams.
- MHRA held analytical software (where possible) will be used for review of analytical data.

Hybrid Inspection

- Activity split between remote and onsite.
- Sites will be asked to provide analytical in advance of the inspection.
- MHRA held analytical software (where possible) will be used for review of analytical data.

When will the different types be used?

- Dependant on several factors:
  - Compliance and inspection history of the site.
  - Nature of the inspection (e.g. routine or triggered)
  - Suitability of the inspection site.

Feedback from Remote and Hybrid Inspections

Use of Visual Technology

- Ensure sufficient connectivity throughout the facility (i.e. wifi, 4G etc)
- Consider how movement between areas will be managed.

Time zone challenges

- Discuss as part of the planning process with your lead inspector.
- Agree when colleagues will be available to support the inspection

Feedback from Remote and Hybrid Inspections (2)

Providing analytical data

- Make use of provided guidance from the Lead Inspector
- Share any challenges you are encountering

Inspection progress

- Agree feedback sessions with your Lead Inspector (usually beginning or end of day)
- Inspectors will share feedback throughout the inspection

Feedback from Remote and Hybrid Inspections (3)

During the inspection

- If the use of a system or process during a hybrid or remote inspection is proving challenging, then raise this with your Lead inspector

Summary

- We have embedded new tools used during the pandemic into routine inspections.
- We continue to look for new ways to improve remote and hybrid inspections.
- Your feedback and inspection experience is welcomed.
- The aim of the inspection, regardless of type, remains the same.

Questions?

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