Medicines & Healthcare products
Regulatory Agency

GLP MONITORING AUTHORITY

CHARLES RIVER LABORATORIES EDINBURGH LIMITED INSPECTION REPORT

Inspection & Organisation Information	
Inspection Number	Insp GLP 1634/25448-0041
Type and Purpose of Inspection	Statutory GLP Compliance Monitoring Inspection
Organisation Inspected	Charles River Laboratories Edinburgh Limited
Organisation Address	Elphinstone Research Centre Tranent Edinburgh EH33 2NE Clearwater House, Research Avenue North, Riccarton EH14 4AP
Organisation Type	Contract Research Organisation (CRO)
Dates of Inspection	12-14 November 2024
Lead Inspector	[redacted] Inspector
Accompanying Inspector(s)	[redacted]
Date of Closing Meeting	14 November 2024
Inspection Report Date	19 December 2024

Relevant Background

This inspection was conducted as a statutory routine GLP compliance monitoring inspection of the Elphinstone Research Centre and Clearwater House facilities.

Inspection Deficiencies

1.0 Critical Deficiencies

None.

2.0 Major Deficiencies

2.1 Archiving

There were a number of studies which had been transferred out from the Test Facility for Archiving at the Sponsor, but no verified copy was taken to ensure review was possible during the inspection, which was not in line with published UK GLPMA guidance (Retention of study data and supporting records for inspection purposes, January 2015). This practice was documented in the facility's [redacted] section [redacted] effective 24 March 2023). However, in the absence of verified copies or enhanced oversight by the Test Facility the studies were not considered to be archived. This was noted to affect 80 studies for Sponsor [redacted] since November 2022.

In addition, discrepancies with the above SOP were also noted:

- The return from the Sponsor was to take place within 24 hours per agreement, however in practice the return took more than 48 hours for the requested study ([redacted] to be provided for inspection.
- The SOP also required that each return occasion to the Sponsor was to be lodged with an agreement which was not the case for study [redacted].

2.2 Test & Reference Control

2.2.1 Test Facility procedures did not include sufficient detail to ensure the OECD advisory document 19 on 'Good Laboratory Practice on the Management, Characterisation and Use of Test Items' requirements to verify the quality and integrity of information provided for characterisation were fully met. Section 7.2 paragraph 40 of OECD 19 states that "Test Facility Management should ensure that documented procedures are in place to verify the integrity and quality of the information provided". Whilst [redacted] version [redacted] effective 09 December 2022) stated in section [redacted] that characterisation should be supported by suitable documentation, there was no further detail on requirements for validity or quality checks.

There was no available documentation which confirmed that checks were performed on received information for test items, and during interview with Study Directors (SDs) it was described that there were no active evaluations of the source of characterisation and documentation received. Examples of the lack of evaluations were found for the following studies:

- [redacted] There was no documentation to detail the checks performed on the Certificate of Analysis (CoA) provided by the Sponsor.
- [redacted] The study plan stated that a GLP Certificate of Analysis (CoA) would be received but the file for the active study only included a CoA from a Contract Research Organisation (CRO) located in a non-OECD MAD (Mutual Acceptance of Data) country. No documentation of any associated checks was available in the raw data, nor any exclusions from GLP compliance documented in the report.

- [redacted] Discrepancies were noted regarding test item characterisation in this study as evidenced by:
    - Different descriptions of the test item were identified across the raw data and final report, with a lack of supporting documentation available to demonstrate checks by the SD had been conducted to explain the below discrepancies:
        - Described as a "suspension" in the CoA (dated 29 June 2021).
        - Described as a "transparent to opaque liquid" in the study plan, amendments and phase plan.
        - Described as a "liquid" in the final report but remained described as a “transparent to opaque liquid” in the phase report.
    - The "advance shipment of TI form" included an entry for "GLP certificate of analysis" which was ticked as “Yes”, however the associated “Test Item Data sheet” conversely stated this had been produced in a GMP facility using a scaled down version of the GMP process.
    - Documentation demonstrating the SD had actively assured themselves of the quality and integrity of information provided supporting the claim that the CoA was produced in a facility under a “pared down GMP quality system” was not available when requested.

3.0 Other Deficiencies

3.1 Archiving

3.1.1 There was no documentation available which included positive confirmation that the SD was satisfied that the electronic archiving was complete, and that which was archived on their behalf by IT were the complete records and study file.

3.1.2 There was an issue with the screen shot retained as evidence of electronic archiving of [redacted] system data. The file provided to the SD and Archivist via email as evidence was from the [redacted] system.

3.2 Computer System Validation

3.2.1 The [redacted] data flow provided for the [redacted] using the [redacted] system was inaccurate in that the automated saving of raw data electronic files [redacted] o the [redacted] was not reflected, despite this step being described under interview as also occurring in this flow (in the same manner as the alternative Integration Manager Import pathway).

3.3 Data Integrity Controls

3.3.1 There was no formal mechanism to meet OECD advisory document 22 (GLP Data Integrity) ‘manual recording’ requirements (detailed in section 6.2), despite the Test Facility using a large number of paper proforma and blank narrative sheets for recording of raw data without

reconciliation or additional control measures. A new study type identified on study [redacted] containing numerous blank, uncontrolled narrative sheets was noted as a pertinent example.

This finding has not been classified as major due the presence of a risk assessment identifying this as a high-risk area with an ambition to resolve this issue via means such as [redacted] however there were no timelines associated with this solution and the justification in the DIRA which stated it was 'impractical' to reconcile paper was not considered suitable.

3.3.2 Gaps in data integrity controls for the processing of [redacted] raw electronic data were identified on study [redacted], where the [redacted] data report was erroneously saved by the analyst to an [redacted] drive rather than the protected [redacted] drive. The issue remained unidentified for three days until a deviation [redacted] was raised upon discovery which stated there had been 'no impact' as the [redacted] report had been moved to the correct drive. However, the deviation documentation and resultant corrective actions had not included any investigation, root cause analysis or implementation of preventative actions to prevent recurrence. In addition, checks on the integrity of the data for loss or alteration (for example via widely available [redacted] editing software) had not been performed, nor prompted any changes to the current QC process which directs quality checks (QC) on [redacted] print-outs instead of source electronic raw data.

3.4 Laboratory Facilities and Equipment

3.4.1 Calibration documentation provided for check weights [redacted] noted during the facility tour at Clearwater House only included an assessment at one weight level, however [redacted] effective 9 August 2024) stated that check weight calibrations would be performed as per section [redacted] of the SOP which required three levels (low/mid/high) to be performed. As part of this response the facility is requested to assess any potential wider impact of this issue, for example in cases where weights may have been out of specification, and if this practice was in wider use at the facility.

3.5 Record Keeping / Essential Documents

3.5.1 Deviation number [redacted] was inconsistent in its description in that it stated that SET 1 of plasma sample was spilled, however the SD impact assessment stated that a FULL SET 1 was obtained.

3.5.2 The location detailed on the [redacted] balance calibration [redacted] certificate was incorrect. The balance full ID [redacted] was detailed as located in Block [redacted] on the external calibration certificate however it was confirmed during the inspection that this was expected to be Block [redacted].

3.6 Reporting

3.6.1 The final report for study [redacted] referenced a publication "([redacted])" in section 4.1.1 to support the rationale provided regarding the suitability of the positive control, however this publication was not listed in the references section of the report despite underpinning key acceptance criteria of the test system.

3.6.2 The Quality Assurance statement for study [redacted] contained a non-descriptive term for the critical phase as 'Sample Analysis' that did not accurately reflect the phase inspected, which was confirmed to be the determination of bulk density for disturbed soil.

3.7 Source / Raw Data

3.7.1 The following issues were noted with raw data recording / form completion as indicated below:

- Study [redacted] – pretreatment [redacted] entries "day number" field was blank on 11 July 2022.
- Study [redacted]
  - The narrative sheets in the text section of file 2 used inconsistent templates. Page 1-7 were uncontrolled templates whereas pages 8-11 used [redacted]
  - The identifiers for equipment timer (page 8), thermometer (page 9) and oven page 9 were not recorded, which was inconsistent with other category B equipment such as the oven on page 10 which was recorded as [redacted]
  - No identifier was recorded for the balance used for dry solids weighed on 04 September 2024 for the Particle Size Distribution section.
- Study [redacted]
  - Overwriting of 24 to 25 was noted on page 1 of the Confirmation of sample receipt [redacted] tracking) form dated 25 April 2024 without error coding or explanatory comment.
  - The certified copy present for the 02 May 2024 Confirmation of sample receipt form was noted to have truncated comment A signature and date.

3.8 Standard Operating Procedures

3.8.1 [redacted] version [redacted] effective 05 January 2024) stated in section [redacted] that the soil classification would be performed manually by plotting points on the textual classification triangle. However, this was performed electronically for the study [redacted]

3.9 Study Management and Conduct

3.9.1 In study [redacted] it could not be reconstructed what was considered the source for comparison of the Quality Control soil sample. [redacted] (version [redacted] effective 05 January 2024) section [redacted] stated that "the QC sample must be within +/- 5 standard deviations for each fraction using current values", however two sources of comparison existed – the original external source [redacted]) and that of the original validation study.

Report Author and Reviewer

Report Author:

[redacted]
[redacted] Inspector
UK GLP Monitoring Authority & MHRA

Report Reviewer:

[redacted]
[redacted] Inspector
UK GLP Monitoring Authority & MHRA

Appendix I – Deficiency Definitions

Deficiency Definitions (GLP)

Critical:

a) Where evidence exists that significant departure(s) from the Principles of GLP has occurred resulting in:
   - i) the test facility, or a part thereof, or a study is not in compliance with the Principles of GLP and/or
   - ii) the study data are unreliable and/or
   - iii) a combination of several "Major" findings (defined in (c)) across the basic GLP quality systems, indicating a systemic quality assurance failure, and/or

b) Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (c))

Major:

c) A non-critical finding where evidence exists that a significant departure from the Principles of GLP has occurred:
   - i) that may not have developed into a critical issue, but if not addressed immediately may lead to a facility, system or study being out of compliance, and/or
   - ii) where evidence exists of a failure of one of the basic GLP quality system elements, and/or
   - iii) a combination of several "other" findings, none of which on their own may be major, but which may together represent a major finding

Other:

d) Where evidence exists that a departure from the Principles of GLP has occurred, and/or established guidelines and/or procedural requirements but it is neither Critical nor Major