Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

INSPECTION REPORT

Labcorp Early Drug Development Laboratories Limited

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Harrogate
North Yorkshire
HG3 1PY

And

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SECTION A INSPECTION REPORT SUMMARY

Inspection details	
Scope of Inspection	Routine compliance monitoring inspection
Name of site contact	[redacted]
E-mail address	[redacted]
Was another inspection (e.g. GLP or GCP) conducted at the same time:	No
Date(s) of Inspection:	15-18 February 2021 (remote) 08-09 March 2022 (onsite)
Lead inspector:	[redacted] inspector
Accompanying Inspector(s):	N/A

Scope of GMP certificate	
Microbiology: sterility	
Microbiology: non-sterility (includes LAL testing)	
Chemical/Physical	✓
Biological (Tests involving animals or animal derived tissue systems including ELISA, SDS page etc.)	✓
Approximately how many live licences is the laboratory named on?	Harrogate- 14 York-1
Other quality systems in place	GCP and GLP (Harrogate only).
Scope of testing	
Active pharmaceutical ingredient (API)	X
Excipients	
Packaging components	X
Finished Product (FP)	X
Investigational Medicinal Product (IMP)	X
Stability (FP)	X
Stability (IMP)	X
In process bulk (powder blends, tablets)	X
Environmental Monitoring for third parties	
Process waters	
Identification of microbial isolates for third parties	
Method Development	X
Method Validation	X
Percentage of work meeting the criteria for inspection based on numbers of batches tested?	[redacted] work is GMP.

SECTION B GENERAL INTRODUCTION

B1 Background Information

Labcorp Early Drug Development Laboratories Limited is a large US based global contract research organisation offering drug development solutions from pre-clinical testing through to clinical trials and CMC support. The York and Harrogate sites (formerly known as Covance) has been owned by Labcorp since 2015 and following the purchase of Envigo now operates a number of sites within the UK. In 2021 it was announced that the Huntingdon site was to be decommissioned and GMP activities transferred to Harrogate and York.

Previous Inspection Date(s):	14-15 June 2017 (Harrogate) 20 February 2018 (York)
Previous Inspectors:	[redacted] (Harrogate) [redacted] (York)

B2 Inspected areas

Topic	Reviewed Yes	No	Briefly
Quality Management			
Technical agreements	X		
Out of Specification results and anomalous results	X		
Deviations	X		
Complaints	X		
Change control	X		
Self-inspection	X		
Staff training			X
Document Control (SOPs, methods, specifications)	X		
Facilities			
Equipment calibration and maintenance	X		
Use of computerised systems	X		
Sample handling (receipt and storage)	X		
Handling chemicals and reagents (including reference substances)	X		
Test Data			
Production and approval of reports and certificates of analysis	X		
Review of data	X		
Retention of data	X		

Limitations / exclusions to inspected areas

Due to COVID-19 travel restrictions, the facilities and equipment supporting Physical/chemical testing was toured remotely.

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

B4 Documents submitted prior to or taken during the inspection:

As this was a partially remote inspection a pre inspection dossier was supplied to the site and all applicable documents were provided. Throughout the inspection further requests for maintenance records and records of QMS implementation were made and supplied. Two data packs were also requested.

No documents were retained from the March 2022 onsite portion of the inspection.

SECTION C INSPECTOR'S FINDINGS

C1 Summary of Significant Changes

Changes since previous inspection which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

[redacted] has been changed from [redacted] to [redacted].

[redacted] has replaced the [redacted] system to log QMS KPI.

Future planned changes which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

The company are in the process of installing a new LIMS system with the aim to automate report production.

The facility are currently in the process of transferring GMP work from Huntingdon. At the time of the inspection this was approximately 40% complete.

No further significant changes are planned.

C2 Action Taken Since the Last Inspection

All actions had been appropriately addressed.

C3 Pharmaceutical Quality System

Out of Specification Results

Out of Specifications are managed by SOP [redacted] effective 14 Sept 2020. The following investigations were reviewed during the inspection:
In relation to Phys/Chem testing

[redacted] Raised following an out of specification result for sub visible particle counts.
[redacted] Raised following unexpected peaks in chromatograms including blanks.
[redacted] Raised following low recoveries in content uniformity.
[redacted] Raised following an atypical result for sample preparation.
[redacted] Raised following the identification of an addition peak when compared to the reference material.

In relation to Biological testing

[redacted] Raised following OOS Result Generated for [redacted] in Assays [redacted] & [redacted] bioassay.
[redacted] Raised following OOS result generated for [redacted] sample [redacted] T=6M 25C on assay [redacted]
[redacted] Raised following [redacted] OOS for [redacted]
[redacted] Raised following an OOT result for [redacted] T=6M 5°C. The analyst had not followed the analytical protocol and reviewed the reference standard, which had not met the specified criteria. The documentation contained potential hypothesis for the failure of the reference control [redacted] Raised following an OOT result for [redacted] T=14 Weeks 25°C.

Out of specification investigations were appropriately managed and conclusions supportable.

Deviations

Deviations were managed via [redacted] effective 25 Jun 2020. The following deviations were reviewed during the course of the inspection:

In relation to Phys/Chem testing
[redacted] Raised following the failure of stability chamber mapping.
[redacted] Raised following a software error preventing the saving of data.
[redacted] Raised following non-compliant installation of safety cabinets.
[redacted] Raised following the failure of a supplier to adequately complete documentation.
[redacted] Raised following failure to complete testing within the specified timescale.

In relation to Biological testing

[redacted] raised following incorrect data reporting for [redacted] qPCR and [redacted] and [redacted] qPCRs.
[redacted] raised following the failure to generate valid genomic titre QPCR results at T=18 months for stability study [redacted]
[redacted] Raised following the use of unqualified reagent in multiple assays.
[redacted] Raised following the duplicate saving of electronic files in [redacted] The root cause was attributed to the first time use of the system by two members of staff, but the investigation did not consider why the staff were working on a system unsupervised.

The scope of investigations into deviations and out of specifications was appropriate and considered all expected aspects. The documentation associated with the investigations did not always include the rationale for the lack of CAPA raised, however when discussing this with site it was clear that appropriate control measures already existed.

CAPA

CAPA's were managed via [redacted] effective 06 Feb 2020.
CAPA's associated with the out of specifications and deviations were reviewed. CAPA management had improved from the previous inspection through a combination of weekly triage meetings and easier access to KPI from [redacted] Extensions to CAPA deadlines had to be agreed by QA and would only be authorised in the event that the CAPA owner could demonstrate active management of their actions.

CAPA adherence in 2020 was approximately 50%, mainly due to the Global Business Technology (IT) implementing CAPA's in relation to data integrity remediation measures. This had been escalated and QA were meeting with GBT leadership fortnightly to manage the process.
As control measures were in place and progress had been made a deficiency was not raised.

Management Review

Management reviews were held quarterly and attended by senior members of QA as well as the testing departments. Meeting minutes from 2020 were reviewed and were deemed appropriate.

Change Control

Change controls were managed via [redacted] effective 14 Sept 2020.

The following change controls were reviewed during the inspection:

[redacted] Raised to change an analytical method.
[redacted] Raised to correct a rounding error in a [redacted] report.
[redacted] Raised to remove the semi annual [redacted] test as part of the dishwasher maintenance.
[redacted] Raised to convert the [redacted] cell banking suite to [redacted]
[redacted] Raised to cover the [redacted] potency stability assessment at 16 months for drug product
[redacted] Raised to cover the temporary storage of consumables and reagents outside of the CMC footprint.
[redacted] Raised to update the temperature deviation assessment criteria for liquid nitrogen storage. It was noted that this change control did not have an effectiveness check assigned, which was deemed inappropriate based on the potential impact.

Change controls were well managed and extensions, as well as the rationale for the extensions could be tracked. The facility were planning to implement a triage system similar to the CAPA to manage overdue change controls or those with protracted extensions.

C4 Personnel

Staff training was not reviewed in detail at this inspection. The review was limited to confirmation that training required as part of CAPA were performed.

C5 Premises and Equipment

Tours of all facilities to support Phys/Chem testing were performed remotely, but physical tours of the York laboratories and the Biological testing laboratories at Harrogate were performed. All facilities were deemed as fit for purpose.

[redacted] (subject to change control [redacted]) was toured and there was appropriate segregation of PCR activities to minimise cross contamination. Cleaning procedures for this area were discussed and deemed fit for purpose.

The temporary storage containers were visited during the inspection. It was noted that the storage conditions for ambient were set at 10-30 degrees Celsius. Within the contained PCR reagents with storage conditions of 15-25 degrees were found. There was no documented jusitifcation for the storage of these reagents in the container and temperature records demonstrated a lack of adherence to the stricter 15-25 degrees.

C6 Documentation

Each batch of product was tested under a study number which detailed the test to be performed, and referenced the analytical methods. Analytical method were issued as controlled copies. Paper copies of analytical methods were only issued when all previous copies were accounted for and destroyed.

The following data was reviewed remotely during the inspection in February 2021
[redacted] HPLC
Study [redacted] covering the analysis of [redacted] and [redacted] The review was limited to the Chromatography assessment of [redacted] oxidation by [redacted] and RP-UPLC

The following data packages were reviewed on site in March 2022.

[redacted]batches [redacted] The data for the Cell based bioassay, subvisible particulate matter determination and size exclusion chromatography was reviewed. The certificate of analysis for the batches were correct and included full details on the methods used and the specification versions. The data from the microbiology subcontractor was also included and clearly identified.

C7 Technical Agreements and Outsourced Activities

Technical agreements were managed through procedure [redacted] effective 24 December 2020. The following quality agreements were reviewed during the inspection:

[redacted] version [redacted] effective December 2020.
[redacted] version [redacted] effective February 2021
[redacted] effective August 2017
[redacted] effective September 2012.

C8 Complaints

No complaints had been received since the last inspection.

C9 Self-Inspection

Self inspections were managed by [redacted] version [redacted] effective 30 March 2020.

The 2019 and 2020 audits were conducted in line with the scheduled dates, any deviations were typically minor and had impact assessments performed. Audits were closed when all actions had been completed and any overdue actions were followed up on a regular basis and escalated as required (an example of this being Global Business Technology as mentioned earlier in the report).

C10 Sample Handling and Control of Reagents (including reference substances)

Analytical reference standards were managed via [redacted] effective 17 October 2019. The procedure was reviewed but the onsite management of reference standards was not covered during the inspection and this will be followed up at subsequent inspections.

C11 Computerised Systems

The data integrity risk assessment for the [redacted] software was reviewed. The facility had performed a risk assessment and implemented actions appropriately mitigate risks identified.

SECTION D DEFICIENCIES

1. CRITICAL

None

2. MAJOR

None

3. OTHER

3.1	The following deficiencies were associated with the change control system:
3.1.1	The records to support the fumigation of lab block [redacted] performed as part of change control [redacted] could not be located during the inspection.
3.1.2	No effectiveness check was performed for change control [redacted] raised to address inappropriate temperature deviation assessment.
EU GMP	Chapter 4 Principle, C1.4(xiii), C4.10
3.2	In relation to the laboratories and facilities:
3.2.1	An expired batch of protein desalting spin tubes was found in a reagent cabined during the tour of the York facilities.
3.2.2	[redacted] DNA mini kits required temperature storage between 15-25˚C but were stored in a contained with an acceptable temperature range of 10-30 ˚C with no justification.

EU GMP	Chapter 6 Principle, C6.21
3.3	In relation to quality events:
3.3.1	The root cause assigned for [redacted] was that there was insufficient staff, but there was no justification for a lack of CAPA raised to address this.
3.3.2	The root cause for [redacted] for duplicate saving of electronic files was that staff had not used the [redacted] system but there was no assessment of why the staff were working untrained on a system and there was no justification for a lack of CAPA raised.
3.3.3	It was not possible to reconstruct the investigation captured in GMP Quality Issue Report [redacted] against the activities performed during the investigation. This specific deficiency was reported within the interim report issued in 2021 and no response is required.
EU GMP	Chapter 4 Principle, C1.8(vii), C4.8

SECTION E SITE OVERSIGHT MECHANISM

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme	✓	N/A	N/A
Compliance Management Team	N/A	N/A	N/A
Inspection Action Group	N/A	N/A	N/A

Section F Summary and Evaluation

F1 Closing Meeting

Deficiencies were accepted.

F2 Assessment of response(s) to inspection report

A single request for additional information was made and addressed by the facility.

F3 Documents or Samples Taken

None.

F4 Final Conclusion/Recommendation, Comments and Evaluation of Compliance with GMP and GDP

The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
The Human Medicines Regulations 2012 (SI 2012/1916)	✓
The Veterinary Medicines Regulations 2013 (SI 2013/2033)	✓
The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)	✓

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date: 19 May 2022**

Accompanying Inspector: N/A **Date:** N/A

Appendix 1

Contract GMP QC Testing Laboratory Risk Assessment

(a). Inspection Findings			
Critical deficiencies this inspection:	0	Critical deficiencies Last inspection:	0
Major deficiencies this inspection:	0	Major deficiencies Last inspection:	0
Other deficiencies this inspection:	3	Other deficiencies Last Inspection:	7

(b). Provisional Rating based on Inspection Output (✓ applicable box)			
Risk rating level	**Input from Current Inspection Findings** (last inspection findings applicable to rating IV only)	**Provisional rating – this**	**Final rating Last**
0	Serious triggers outside the inspection cycle	[redacted]	
I	Critical finding		
II	2 or more Major findings		
III	1 Major finding or 5 or more others		
IV	No Critical or Major findings from current and previous inspection and less than 5 other findings on this occasion.		

(c) Risk Assessment Inputs – discriminatory factors (✓applicable box)	
[redacted]	None relevant (default)
	Significant concern over robustness of quality system to retain adequate control
	Significant failures to complete actions to close previous deficiencies raised at the last inspection
	Complex site
	Significant changes reported in Compliance Report
	Significant mitigating factors applied by the site
	Higher risk rating identified by other GxP and considered relevant to the GMP site
	Relevant site cause e.g. recalls, notifications to DMRC since last inspection
	Regulatory action related to the site
	Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments from post inspection action plan
	First Inspection by MHRA (does not require countersignature for RR II)
	Other discriminatory factor (record details and justify below)

(d). Inspector's Supporting Information/ Justification Relating to additional Factors
[redacted]

(e). Risk Rating Result Incorporating Discriminatory Factors (✓ applicable box)		
Risk rating level	**Recommended Inspection Frequency**	**Inspector Proposed Risk Rating (✓)**
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	18 months	
III	30 months	
IV	36 months	

(f). Basis for risk-based acceptance of specific matters arising during the inspection:

[redacted]

(g). GMP conditioning remarks required

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments (Risk rating level 0, I, II):

[redacted]

(j). Confirm Agreed Risk rating following this inspection:

Risk rating	Days on site	Next inspection target date
[redacted]		

Notes regarding re-inspection and GMP certificate validity

1. The inspection schedule is based upon risk and resource. This date may change at any time due to factors not pertaining to your site.
2. The GMP certificate does not 'expire' it is provisionally assigned 3-year validity date. For external questions regarding your validity thereafter; please advise that this can be confirmed by contacting the inspectorate at gxplabs@mhra.gov.uk