



INSPECTION REPORT

ARC PHARMA (UK) LIMITED

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SECTION A INSPECTION REPORT SUMMARY

Inspection details	
Scope of Inspection	Routine Inspection – Remote inspection performed due to covid-19 travel restrictions
Name of site contact	██████████
E-mail address	████████████████████
Was another inspection (e.g. GLP or GCP) conducted at the same time:	No
Date(s) of Inspection:	14 th to 17 th September 2020 (equivalent to 1 days)
Lead inspector:	██████████
Accompanying Inspector(s):	N/A

Scope of GMP certificate	
Microbiology: sterility	N/A
Microbiology: non-sterility (includes LAL testing)	N/A
Chemical/Physical	✓
Biological (Tests involving animals or animal derived tissue systems including ELISA, SDS page etc.)	N/A
Approximately how many live licences is the laboratory named on?	████ Manufacturing Authorisations and █████ Marketing Authorisations
Other quality systems in place	No

Scope of testing	
Active pharmaceutical ingredient (API)	✓
Excipients	✓
Packaging components	N/A
Finished Product (FP)	✓
Investigational Medicinal Product (IMP)	✓
Stability (FP)	✓
Stability (IMP)	✓
In process bulk (powder blends, tablets)	✓
Environmental Monitoring for third parties	N/A
Process waters	✓
Identification of microbial isolates for third parties	N/A
Method Development	✓
Method Validation	✓
Percentage of work meeting the criteria for inspection based on numbers of batches tested?	80% of work performed on site is finished product testing.

SECTION B GENERAL INTRODUCTION

B1 Background Information

The company was set up in 2014 and moved to the current premises at the end of 2018. The main focus of the laboratory is the physical chemical testing on finished marketed products, most of which are being imported from [REDACTED]. The laboratory subcontract microbiology testing to [REDACTED] on behalf of contract givers e.g. [REDACTED]. X ray defraction testing is subcontracted to [REDACTED].

The lab has grown significantly over the past few years and at the end of august 2020 had tested [REDACTED] batches overall. The staff numbers have grown since the last inspection to 38 (QA team of 8 and QC Team of 25.)

Previous Inspection Date(s):	10 th & 11 th January 2019
Previous Inspectors:	[REDACTED]

B2 Inspected areas

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

Limitations / exclusions to inspected areas

Remote Inspection performed during covid-19 travel restrictions, physical inspection of facilities and equipment was not possible.

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
██████████	██	██████████
██████████	██	██████████
██████████████████	██	██
██████████████████	██	██████████████████
██████████	██	██████████████████

B4 Documents submitted prior to or taken during the inspection:

A completed pre inspection compliance report and organisation chart were provided along with copies of SOPs identified in the notification letter including among others, those relating to management of deviations and out of specification results, self-inspection, and change control. Deviations, CAPA, OOS and change control logs since the last inspection were also provided.

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:

██████████ ceased 05/12/2019 as significant control and ██████████ and ██████████ added as shareholders, no impact on business.

There has been a significant increase in staff with 14 new analysts and 4 new QA officers joining the company

The instrument lab has been expanded with additional HPLC, GC, IC and UPLC installed and dedicated area for oncology/cytotoxic product handling and dedicated secure paper documentation storage area

Addition of █ more ██████████ HPLC, █ GC, █ Analytical balances, █ pH meters, some sonicator, centrifuges, █ UV, █ dissolution bath, thermometers, stability cabinets

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

C2 Action Taken Since the Last Inspection

Inspection findings from last inspection had been appropriately addressed with the exception of 3.2 which is discussed in section C3 CAPA.

C3 Pharmaceutical Quality System

Out of Specification Results

effective 05 Jan 2019 –

There were 39 OOS investigations raised following the last inspection. For all investigations there was no obvious laboratory error, root causes were predominantly “due to stability” at the end of shelf life.

related substances test found to be OOS at the end of shelf life.

assay by HPLC OOS lead to an investigation by

The was no evidence to demonstrate that steps of the hypothesis test plan around the homogeneity of the crushed had been performed in wither the worksheet or investigation report.

the following tests were OOS with no obvious laboratory error
Assay/CU/Dissolution by HPLC.

microbial testing was out of trend no obvious laboratory error. Communication was established between all three parties (customer, within appropriate timescales. Consideration should be given to attaching email communications where critical steeps in the investigation process are discussed and made to the final report.

related substances by HPLC found to be OOS at end of shelf life.

Deviations

There two methods of dealing with non-conformances, deviations and incidents covered by 2 separate SOPs.

effective 05 Jan 2019 –
effective 05 Jan 2019 –

– Raised as incorrect units reported on C of A for batches

– Raised for the external calibration of a cold chain data logger.

The corrective action implemented to provide temperature monitoring was not risk assessed and the instructions for how it would be carried out was not appropriately documented. Furthermore, no preventative action has been implemented to prevent a similar occurrence in January 2021.

██████████ – Raised because although █████ failed testing was continued and reported for information only.

██████████ - Raised following a deviation at partner lab during microbiology testing of ██████████ for ██████████. On review of email communications from the contract giver it is clear appropriate action was taken.

CAPA

██████████ effective 05 Jan 2019 - ██████████
There were 4 CAPA raised in 2019 and 1 to date in 2020 with all being the outcome of an audit. No explicit instruction to perform post effectiveness checks in ██████████ however a post effectiveness check is included on the CAPA proforma.

██████████ – MHRA inspection actions

Finding 3.2 of the previous inspection found that *'there is no definition of when an issue is regarded as an incident, therefore it is unclear which procedure should be followed.'* The effective dates for these SOPs have not changed since the previous inspection and the commitment to update and elaborate on their use has not been carried out. During discussion it was agreed that a clarification will be added to one of the SOPs to clarify when each one should be used.

██████████ – Customer Audit by ██████████ (raised 16 May 2019) 2 actions around acceptance criteria for melting point standards and of recommendations for temperature mapping of the fridge/freezer.

██████████ – customer audit by ██████████ raised 21 Jan 2020) two actions around calibration of glassware and access to the archive area.

During discussion about the finding around archiving and the current ██████████ effective 06 Jan 2019 - ██████████ it became apparent that the action had not been appropriately risk assessed and that there was no way of tracing who had entered the archive area, why they had entered, what they had removed and whether the document had been returned or destroyed.

Regulatory Updates

The BP is reviewed annually, and it was confirmed the 2020 BP review had been performed and confirmed no impact.

Management Review

SOP ██████████ effective ██████████

The quality review meeting is held twice a year and minutes from October 2019 and February 2020 and the quality improvement plan were reviewed and discussed. The quality improvement minutes were identified at the February review meeting with progress Tracked by █████ and reviewed at the QRM meeting. A conversation was held around the minutes and it was suggested that consideration should be given providing more detail on what was actually reviewed and to also including severity rating and number of overdue items in the metrics. It is acknowledged that at the time of the inspection that the present the level of CAPAs/Dev/OOs etc. are low and easy to track and manage.

Change Control

██████████ effective 05 Jan 2019 - ██████████

The following were reviewed and found to be acceptable

– Raised to manage the project to install additional equipment/stability storage cabinets and create a cytotoxic product testing area.

– Addition of a new product in the client folder.

– Specification change for

– Raised to add a new client

Analytical Method transfer

effective 06 Jan 2019 -

The following analytical method transfer activities were reviewed.

Protocol Ref & Report

Protocol & Report

In both of the above cases there was no justification to support performing a single dissolution test as part of the analytical method transfer.

C4 Personnel

The lab has grown significantly over the past few years and at the end of august 2020 had tested batches overall. The staff numbers have grown since the last inspection to 38 (QA team of 8 and QC Team of 25.)

The training module was reviewed on the system via SOP training and refresher training and external technique and QMS training was observed and found to be appropriate.

Job description for and analyst qualification protocol reviewed and found to be acceptable pack.

C5 Premises and Equipment

Remote Inspection performed during covid-19 travel restrictions, physical inspection of facilities and equipment was not possible.

C6 Documentation

The system was demonstrated via and it was observed how methods and specifications are updated in a controlled manner.

Certificates of analysis observed during deviation and OOS review were found to be acceptable.

Data packs were reviewed for the following batches

The test procedure was reviewed for document ref
effective 12 Feb 2020

C7 Technical Agreements and Outsourced Activities

effective 06 Jan 2019 -

All technical agreements were within their review date and the following technical agreements were reviewed.

The technical agreements with did not detail who was responsible for the trending of data.

C8 Complaints

effective 06Jan 2019-

There had been 3 complaints since the last inspection all were around entries on certificates of analysis.

– raised as the incorrect customer batch number had been recorded during sample receipt and reported on the C of A.

– raised as the incorrect customer batch number had been recorded during sample receipt and reported on the C of A.

raised as the expiry had was incorrect on the C of A nstead of

C9 Self-Inspection

SOP effective 06 Jan 2019

Self-inspection was performed once a year by an external auditor and covered the following areas QMS, QC analytical and Training. The external inspector is provided by and was a QP. ARC request a copy of the inspector's CV prior to agreeing to them performing the inspection. The scope of the inspection is not defined within the SOP however, the 2019 inspection report was requested along with the CVs of (inspectors) and the service agreement with. The 2019 inspection report is thorough and covers all areas of the QMS and activities performed at the site.

2020 inspection had not been performed at the time of the inspection due to the change in working arrangement brought about by covid-19 pandemic.

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

Not assessed

C11 Computerised Systems

effective 05 Jan 2019

There are several computerised systems on site the amin ones are bespoke system and software associated with UV and FTIR.

Data integrity risk assessments for FTIR and system were requested however these are incorporated into a

This document contains a risk assessment of all QC equipment capable of storing data by asking six key questions. The questions are high level and there is no indication of how each system meets the criteria or what control measures are in place to mitigate the risk. SOP does not include the requirement for a risk assessment to be performed as part of the validation process as required by EU GMP Annex 11.

The following validation documents were reviewed as apart of assessment of DI

SECTION D DEFICIENCIES**1. CRITICAL**

None

2. MAJOR

None

3. OTHER

- 3.1 Dev [REDACTED] raised for the external calibration of cold chain data loggers was not compliant as demonstrated by:
- The corrective action implemented to provide temperature monitoring was not risk assessed and the instructions for how it would be carried out was not appropriately documented.
 - No preventative actions had been considered prior to calibration taking place in January 2021

EU GMP C1.4(xiv), C1.13(i-ii)

- 3.2 The activities performed as part of the CAPA system were not compliant as demonstrated by

3.2.1 CAPA [REDACTED] finding [REDACTED] from inspection findings from the previous inspection in January 2019 had not been completed as agreed.

- 3.2.2 CAPA [REDACTED] regarding access to the archive area
- The action had not been appropriately risk assessed
 - There was no way of tracing who had entered the archive area, why they had entered, what they had removed and whether the document had been returned.

EU GMP C1.4(xiv), C1.13(i-ii), C4.10

- 3.3 Data Integrity of computerised systems was not adequately risk assessed as evidenced by a single overarching data integrity risk assessment. It did not demonstrate an appropriate assessment had taken place to ensure adequate controls were in place for individual computerised systems. The control measures referred to in the risk assessment were not adequately described to demonstrate that identified risks are being mitigated within individual systems.

EU GMP C1.13(i-ii), A11.1

- 3.4 Analytical method transfer activities did not demonstrate that ARC Laboratories could perform testing consistently and reliably as evidenced by; analytical method transfer for [REDACTED] and [REDACTED]

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████████████████████ involved a single dissolution test and therefore reproducibility of the process was not assessed.

EU GMP

A15.5.19, A15.5.20

3.5

The technical agreement with ██████████ did not detail who was responsible for the trending of data.

EU GMP

C7.15

3.6

For ██████████ The outcome of the sample preparation review and additional steps required as part of hypothesis testing, were not appropriately documented at the time they were performed in either the analytical worksheet or the investigation report.

EU GMP

C4.8

4. **COMMENT**

None

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 verbally accepted at the closing meeting.

F2 Assessment of response(s) to inspection report

There were 3 requests for further information which over an extended period due to workload at the laboratory.

F3 Documents or Samples Taken

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

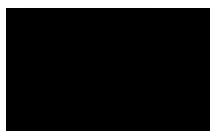
The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
Directive 2001/83/EC, Directive(s) 2003/94/EC and 2011/62/EU	✓
Directive 2001/20/EC	N/A
Directive 2001/82/EC	✓

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector:



Date: 18 November 2020

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:	1
Other deficiencies this inspection:	6	Other deficiencies Last Inspection:	2
(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 assessment	Final rating Last Assessment
0	Serious triggers outside the inspection cycle		
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)			
	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			

(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)	
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:

(g). GMP conditioning remarks required

(h). Conclusions

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

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

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