Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

JC ANALYTICAL 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	[redacted]
E-mail address	[redacted]
Was another inspection (e.g. GLP or GCP) conducted at the same time:	No
Date(s) of Inspection:	7th to 10th September 2020 (equivalent to 1 day)
Lead inspector:	[redacted]
Accompanying Inspector(s):	

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Scope of GMP certificate	
Microbiology: sterility	N/A
Microbiology: non-sterility (includes LAL testing)	✓
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?	25 manufacturing Authorisations and 155 marketing authorisations.
Other quality systems in place	No
Scope of testing	
Active pharmaceutical ingredient (API)	✓
Excipients	✓
Packaging components	N
Finished Product (FP)	✓
Investigational Medicinal Product (IMP)	N
Stability (FP)	✓
Stability (IMP)	N/A
In process bulk (powder blends, tablets)	N/A
Environmental Monitoring for third parties	N/A
Process waters	✓
Identification of microbial isolates for third parties	✓
Method Development	✓
Method Validation	✓

Percentage of work meeting the criteria for inspection based on numbers of batches tested?	95% of work performed ins GMP

SECTION B GENERAL INTRODUCTION

B1 Background Information

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JC Analytical (JCA) was set up in January 2003 as a management buy-out of the former Stafford miller site in Plymouth. JCA moved to a small light industrial unit in Callington in April 2004. In August 2018, the company was acquired by [redacted].

The main activities of JCA are contract analytical services for the pharmaceutical and healthcare industries. This includes the testing of raw materials, chemical and microbiological testing of finished products. The company also provides stability storage facilities and testing to ICH guidelines.

The QA Manager left the company in March 2020 and was replaced by [redacted]

Previous Inspection Date(s):	**10th & 11th October 2018**
Previous Inspectors:	[redacted]

B2 Inspected areas

Topic	Reviewed Yes	Reviewed No	Reviewed Briefly
Quality Management			
Technical agreements			
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			
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

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

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B3 Key Personnel met/contacted during the inspection

[redacted]

B4 Documents submitted prior to or taken during the inspection:

A completed change 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:

The QA manager recently left the company resulting in a restructuring to ensure complete separation of operational and quality responsibilities. [redacted] has moved to the quality team with [redacted] taking over responsibility for the day to day operational activities.

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

[redacted]

C2 Action Taken Since the Last Inspection

Previous inspection findings had not been completed in a timely manner and where they were, there was no evidence to demonstrate completion e.g. [redacted] associated with the traceability of secondary standards. The completion of these actions was being managed via deviation 285 raised in July 2020 as part of a root and branch review of the QMS.

C3 Pharmaceutical Quality System

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The pre inspection compliance report stated that there had been an issue with the effective management of the [redacted] Non-compliance reports and CAPA were raised to deal with this matter. There had been insufficient time between the raising of the CAPA's and the inspection to assess whether they were effective or would address longer term issues with the performance of the QMS. As a major had been raised at the previous inspection relating to the QMS this grading was maintained due to the number of overdue actions and on site follow up will be required within [redacted] months to ensure adequate progress is made.

Out of Specification Results

The proforma [redacted] used for the investigation of [redacted] data is held in a common folder accessible by all staff. Once assigned an investigation reference the proforma is completed electronically but not printed and signed on completion of each entry. The only way to determine when the last entry was made is by the files 'date modified' entry.

This SOP did not cover retesting of the product where assignable cause is not found.

Microbiology Out of Specifications reviewed:

[redacted]

All microbiology out of specifications had been attributed to product and were clearly reported. No stage 2 or 3 investigations had been performed in the above [redacted] to assess.

Chemical Out of Specifications reviewed:

[redacted]

Hypothesis testing was documented retrospectively
Conversation with [redacted] regarding exclusion of an anomalous result was not documented as a CAPA to prevent reoccurrence.

Deviations

Deviations were managed via [redacted] "Control of Deviations".

The following deviations were reviewed during the inspection:
[redacted] – which occurred as a result of not enough sample for a [redacted] reduced sample size to be used.
[redacted] - which also occurred as a result of insufficient sample by received, a smaller amount was tested and used as a 1 in 10 dilution.
[redacted] used as initial diluent for [redacted] was out of date [redacted] review and restructure.

For deviations [redacted] the root cause did not consider all aspects that had led to testing occurring (for example time constraints) and the deviations did not contain sufficient detail to reconstruct events without the assistance of the site.

CAPA

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CAPA's were managed via [redacted] "Corrective and Preventative Action (CAPA)" effective 04 Aug 2020.

The following CAPA's were reviewed during the inspection:
[redacted] Raised following [redacted]. Action [redacted] was due to be completed by the 18 Mar 2019 but was not completed until 29 Aug 2019 and there was no approval for the extension.
[redacted] raised to review registered methods for [redacted] this was a follow on CAPA to [redacted] were raised to restructure the QMS following performance issues. The documents referenced a risk assessment on QA/QC capability and capacity but the risk assessment did not provide any details on an assessment of individuals experiences, competency and any gaps.
[redacted] had a target date of 14 Aug 2020 and no formal extension had been documented as granted.

CAPAs were not routinely closed within the required timescale, this was one of the issues that had led to the restructure of the QA team.

Management Review

Management review was controlled via [redacted] "Management and Quality Review" issued 07 Aug 2020.

The minutes for the monthly quality meeting and 6 monthly management meeting covering June-August 2020 were reviewed. Management meeting minutes did not contain adequate detail on the incidences raised, trending of data or evidence of measures to correct the outstanding issues.

Change Control

Change control was controlled via [redacted] issued 04 Aug 2020 "Change Control".

There was no effectiveness review for change controls prior to [redacted] becoming effective on 04 Aug 2020. No specific actions were included on either the old or new versions for the control forms making it difficult to understand what work had been performed to support the change.

Change controls were not in place for the following

[redacted]

Change controls were not implemented at the start of a process. In the case of equipment or software systems for example [redacted] e.g. introduction of the new [redacted] temperature and humidity monitoring system, the change control was raised following purchase and testing.

With the exception of [redacted] the change controls listed below were all closed at least 10 months after the specified target closure date, and this also applied to completion of the associated actions. However, [redacted] was closed prior to all actions being completed.

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[redacted] update: change to contract giver and acceptor details, update to new template version [redacted]
[redacted] update to include how result is determined and add calculation [redacted] Traceability of reference standards & [redacted] Secondary standard traceability The associated [redacted] does not include documented check of secondary standards and disposal of those not traceable to a compendial chemical reference substance.
[redacted] a new [redacted] temperature and humidity monitoring system was installed with [redacted] successfully undertaken, the new system will run in parallel with the current digitrak system prior to, and after, successful [redacted] This Change control was raised after the work had been performed.

C4 Personnel

There are 16 members of staff split into quality and operational teams. The following training records were reviewed:
Job description and [redacted] nvestigation training for [redacted]
[redacted] investigation training for [redacted]
Microbiology method validation and growth promotion for [redacted].

GMP Refresher training and associated questionnaire for 2019 were reviewed and found to be acceptable. In order to bring new ideas into the company 2020 refresher training will be performed by a third party.

C5 Premises and Equipment

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

Cleaning

The microbiology lab cleaning records for February to September 2020 were reviewed and found to be satisfactory. The records confirm rotation of cleaning agents, areas cleaned and by whom.

The washing machine had been validated. However, the settings for programme 1 were not checked and could not be confirmed to be the same as during original validation.

Temperature monitoring and mapping

Temperature monitoring of rooms and equipment was reviewed. It was noted that the temperature monitoring system, probes and temperature-controlled equipment were not included in the VMP attachment which was a work in progress. Following a discussion around the calibration of temperature probes it was confirmed that there was no evidence to confirm acceptance criteria of 0.25°C. On review of the certificate of calibration for the Freezer it was noted that although action limits were set at -50°C the probe was only calibrated to -40°C. Further discussion confirmed that the freezer only operated down to – 32°c and the SOP and limits will be amended appropriately.

C6 Documentation

The following data packs were reviewed
AMT protocol and Report [redacted] liquid concentrate for pigeons
AMT protocol and Report for [redacted]
Worksheet, Method and [redacted]

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Worksheet, Method and [redacted]
Worksheet, Method and [redacted]

The following additional documentation was reviewed during the inspection.

Microbiological Media Preparation sheets – Actions recorded on these sheets e.g. weighing and pH were not checked contemporaneously.

Balance [redacted] effective 03 Feb 2020) for initials of the person performing the daily check and the peer reviewer were not dated.

Generally documentation was completed to an appropriate standard.

C7 Technical Agreements and Outsourced Activities

All technical agreements were within their review periods with the following reviewed.

[redacted]

The content of technical agreements was generally appropriate. Two small deficiencies were raised relating to the content. See section D for details.

C8 Complaints

There were 2 complaints raised following the last inspection

[redacted] – raised following shipment of [redacted] on dog [redacted] stability samples which were where not labelled properly to the client. The root cause was attributed as human error but there was no documented interview with the analyst.

[redacted] – raised by the client following identification that JCA deviated from the contract givers registered methods for [redacted] The root cause analysis pointed towards systemic failures but did not include justification for why other products were not affected.

The documentation associated with the root cause analysis failed to demonstrate that all systems had been appropriately assessed and that a wider impact could not have occurred. The lack of detail within the documents was discussed with the site.

C9 Self-Inspection

Internal Audit

The schedule consisted of a single annual internal audit. In 2019 this was performed by [redacted] (Commercia Director) at the time) and [redacted] Manager with the report reviewed by [redacted] Operations director. Going forward it is proposed that this will be performed by a third party to ensure independence of the inspector. No self-inspection had been performed in 2018.

Vertical Audit

Vertical audits of processes were to be introduced in 2021 and would be performed on a rolling 24-month schedule.

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

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Sample handling was not assessed as part of the inspection.
Secondary standards were covered as part of review of [redacted]

C11 Computerised Systems

[redacted] (issued 18 Aug 2020) Computerised systems detailed how system access is managed and data backed up.

There were a number of computerised systems in place on site (see list below) SOPs for computerised systems and data integrity were reviewed and found satisfactory.

[redacted]

Data integrity risk assessments were in place for all systems using a proforma spreadsheet with action fed back into a single overarching risk assessment. The actions from all systems were then combined into a [redacted] to 260 with each one used to close out CAPA of a similar severity rating. For instance, [redacted] covered high-risk actions requiring immediate attention while 260 covered long-term medium risk actions. Data integrity risk assessments were reviewed for the [redacted] system along with associated CAPA and found to be appropriate.

SECTION D DEFICIENCIES

1. CRITICAL

None

2. MAJOR

2.1 The quality management system was not fully in control as evidenced by:

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2.1.1 Previous inspection findings had not been completed in a timely manner and where they had there was no evidence to demonstrate completion e.g. [redacted] associated with the traceability of secondary standards to compendial reference standards.

2.1.2 There were 32 CAPAs, 4 Deviations, 8 Out of Specifications and 21 Change controls which were overdue at the time of the inspection.

2.1.3 62 of the facility's 108 SOP's (57%) were overdue for review.

2.1.4 No self-inspection activities were performed in 2018.

2.1.5 There was no evidence to demonstrate routine review of pharmacopoeias to ensure the business remained in compliance.

2.1.6 Management meeting minutes did not contain adequate detail on the incidences raised, trending of data or evidence of measures to correct the outstanding issues.

2.1.7 No CAPA effectiveness checks were performed for [redacted]

2.1.8 The root cause for complaint [redacted] raised following dispatch of unlabelled stability samples to the client, was deficient as follows:

- The root cause was assigned as human error but there was no evidence of assessment of the SOP or training as part of the root analysis.
- There had been no assessment of the wider implications.

2.1.9 The investigation into complaint [redacted], raised following JCA not adhering to registered testing methods did not include an assessment of other test methods or justification that the incident was limited to [redacted] batches.

EU GMP C1.4(xiv), C1.5, C1.6, C4.29, C9.1

3. OTHER

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3.1 The activities performed as part of the out of specification investigation system were not compliant as demonstrated by:

3.1.1 For investigation [redacted]

- The hypothesis testing protocol was documented retrospectively
- No action was recorded regarding the analyst's decision not to report an out of specification result.

3.1.2 It could not be demonstrated that proforma for [redacted] investigations were completed contemporaneously or controlled in a secure manner. The proforma [redacted]) used for [redacted] investigation was held in a common folder accessible by all staff. It is completed by the analyst who requests an investigation reference number form QA. The proforma is completed electronically in a manner that does not facilitate traceability.

EU GMP C1.4(xiv), C4.2, C4.8

3.2 The activities performed as part of the change control system were not compliant as demonstrated by:

3.2.1 Change controls were not implemented at the start of a process, e.g. introduction of a new [redacted] system but were initiated once the process or a decision to make a change had been informally discussed and agreed. In the case of equipment or software systems the change control was raised following purchase and testing.

3.2.2 No deviation was raised to investigate and manage the late closure of a number of change controls, including [redacted] update to method [redacted] traceability of reference standards both of which were associated with CAPA from the previous inspection.

3.2.3 [redacted] raised to manage the introduction of the new [redacted] temperature and humidity monitoring system was closed prior to all of the actions being completed.

EU GMP C1.4(xii), C1.8(vii), A15.11.6

3.3 The following deficiencies were identified with technical agreements:

- The TA with [redacted] required JCA to follow both EU and US GMP however there was no evidence to support an assessment of the differences between the requirements.
- The TA with [redacted] contained the incorrect business address for the contract acceptor.

EU GMP C7.12

3.4 The first 250ml of purified water taken from the tap were discarded prior to performing weekly environmental monitoring (EM) however this process was not performed daily prior to testing therefore the EM

procedure was not representative of laboratory activities.

EU GMP C1.8(iv)

3.5 Analytical method transfer activities did not demonstrate that JC Analytical could perform testing repeatedly because insufficient samples were tested as evidenced by the requirements of SOP [redacted] Aug 2020) which only required a single lot of the item to be tested.

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EU GMP A15.5.19, A15.5.20

3.6 The general glassware cleaning procedure Work [redacted] effective 04 October 2019) has not been validated

EU GMP C6.19, A15.10.1

3.7 There were no defined acceptance criteria for the calibration of temperature and humidity probes.

EU GMP C3.41

3.8 Microbiology Testing for [redacted] defined in [redacted] states the method source was the [redacted] however the method did not follow the EP and was a client registered method.

EU GMP C4.2, C4.3

3.9 The checks performed as part of the media preparation, for example balance ID, weight of reagents, pH etc were not recorded in a timely manner.

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

All responses were found to be acceptable following clarification.

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
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):

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Lead Inspector: [redacted] **Date: 26 October 2020**

Accompanying Inspector: **Date: 29 October 2020**

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:	1	Major deficiencies Last inspection:	2
Other deficiencies this inspection:	9	Other deficiencies Last Inspection:	8

(b). Provisional Rating based on Inspection Output (✓ applicable box)

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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	[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]

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(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

This certificate is issued based on a remote inspection of GMP compliance during COVID-19 travel restrictions. A risk-based site inspection programme remains in force.

(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:

[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