Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

UK CONTRACT GMP QC TESTING LABORATORY

INSPECTION REPORT

Helvic Limited

23-24 October 2018

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

SECTION A INSPECTION REPORT SUMMARY

Inspection details	
Case Folder Reference	Insp GMP/IMP 39630/2968688-0005
Purpose of Inspection	Routine re-inspection
Section 40 Name and address of site inspected	Helvic Laboratories Limited [redacted]
Name of site contact	[redacted]
Tel no	[redacted]
E-mail address	[redacted]
Was another inspection (e.g. GLP or GCP) conducted at the same time:	No
Date(s) of Inspection:	17-19 July 2018
Lead inspector:	[redacted]
Accompanying Inspector(s):	[redacted]
Previous Inspection Date(s):	14-15 July 2015

Scope of GMP activities carried out by laboratory:	Tick
Microbiology: sterility	X
Microbiology: non-sterility (includes LAL testing)	X
Chemical/Physical	No
Biological (Tests involving animals or animal derived tissue systems including elisa, sds page etc)	No
Volume and Type of testing: Approximately how many live licences is the laboratory named on?	163 product licenses. 50 Manufacturing Licenses.

Indicate the manufacturing stage at which the laboratory is testing products and whether the products are marketed or investigational medicinal products	
Raw materials	
Actives (APIs)	No
Excipients	Yes
Packaging components	No
Finished Product	
Marketed	Yes
Investigational (IMP)	Some
Stability	
Marketed	Some
Investigational (IMP)	Occasional
In process bulk (powder blends, tablets)	No
Environmental Monitoring	Yes
Process waters	Yes
Identification of microbial isolates	Yes
Method Development	Yes
Method Validation	Yes

Of the testing carried out indicate how much meets the criteria to be inspected?

All work meets criteria for inspection. The facility conduct approximately 1300 tests per month.

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Details of other activities carried out by the laboratory, including involvement with GLP studies, Human clinical (GCP) trials or ISO [redacted] laboratory accreditation:

None.

SECTION B GENERAL INTRODUCTION

B1 Background Information

The company was initially established by [redacted] to operate as a contract testing laboratory for their own products. Helvic was acquired by Tenatmus UK Limited on 28th of February 2016.
Since the last inspection [redacted] had been appointed as Quality Manager replacing [redacted]
Tentamus group in the UK includes 2 other GMPQC contract testing laboratories [redacted] and FDAS and a further company QTS that tests agrochemicals and foodstuffs. [redacted] who is the technical director and site lead at FDAS is the UK Head for this group of companies within the Tentamus umbrella.
The main bulk of the work is sterility testing.

B2 Overview of the site and the areas used for GMP QC testing

Dedicated room with 2 grade A isolator cabinets and a Bio-safety cabinet
Main open laboratory with benches and cabinets. A small laboratory to the side of the main laboratory was used to house a number of incubators for testing.

B3 Names and job titles of the key personnel who participated in the Inspection:

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[redacted]

B4 Documents submitted prior to or taken during the inspection:

MHRA Laboratory Change report, Deviation, Non conformance, change controls, Out of Specification Listings for 2017-2018.
Facility Procedures: Sterility Test Failures, Specifications Investigation, LIMS Sample Life-Cycle, Process Deviations, Change Control, Documentation Control, Personnel and Organisation Chart

SECTION C INSPECTOR'S FINDINGS

C1 Review of previous deficiencies and corrective actions

All deficiencies had been addressed with the exception of 3.1 relating to the archive of the electronic data from the [redacted] system.

C2 Areas inspected

The inspection included an assessment of personnel, facilities and data. The following processes and procedures were reviewed:

Topic	Reviewed Yes	Reviewed No	Reviewed 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			
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		

C3 Quality management

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Out of Specifications and anomalous results:
Out of Specification is covered by [redacted] The following [redacted] were reviewed and were well managed by the facility.
[redacted] - The conclusion from the [redacted] was that there was no error detectable and the results could not be invalidated. They were therefore reported as failing to meet specification on the [redacted]. Incidences of [redacted] were very low compared to the volume of testing.
[redacted] [redacted] inconsistency between duplicate plates. Both results were in spec but the contract giver requested an investigation and retest because the interpolate variability was high [redacted]
The way in which repeat testing results were reported was raised as a deficiency but the investigative process was considered sound.

Change control
The following change controls were reviewed:
[redacted] – change in raw materials ([redacted] membrane packaging). Delayed change, not due for completion until Nov 2018.
[redacted] – change in [redacted] Currently on hold. The [redacted] for the replacement [redacted] system (produced in Nov 17) was reviewed but had not been updated following the issuance of the MHRA GXP data integrity document.
[redacted] – replacement of isolator in the cleanroom. Currently on hold.
[redacted] – change to personal monitoring procedure when using the isolator. Change from a single contact plate to a [redacted] settle plate and one finger plate per hand. All actions to complete the change had been performed within the predefined timescale. The only comment to note was that the change actions were approved on 04 May 2018 stating that a risk assessment for the change had been written, but that the associated assessment was dated 23 May 2018. There were no concerns regarding the management of change controls.

Deviations and CAPA:
The following deviations, root cause analysis and CAPA were reviewed.

[redacted] – Deviation due to incorrect volume tested. Classified as minor deviation. Root cause determined to be unclear method. [redacted] covering the update of the method validation report, reissuing the individual testing summary and assessing whether other test methods could also be affected were raised as a result and actions were completed within the predefined timescale.

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[redacted] – relating to a lack of timeliness in escalating an error in sterility testing to management. The root cause analysis was that individuals had not followed the procedure however a timescale for reporting was not defined at the time, but [redacted] was updated as part of the CAPA. The records for the supplementary training demonstrated that the individual performing the supplementary training had also not followed the procedure and there was no documented evidence the analyst was in a position to provide the training.
[redacted] – Raised as a result of a [redacted] being released to the client a day before the assay was completed. The facility classed the deviation as minor but in the opinion of the inspector it should have been classified as major due to the failure of contemporaneous recording and two quality control checks. The root cause analysis stated that there was a lack of consistency in the results checking. While supplementary training was issued the procedures were not reviewed and updated to provide further guidance and prevent a reoccurrence therefore a deficiency was raised.

[redacted] – relating to turbidity being observed during a sterility test (days 4 and 13) and samples not being taken for further evaluation. Test solutions were disposed of by the time this was realised. This was identified at the checking stage as part of the documented process demonstrating that process was robust.

Effectiveness checks were performed as part of the CAPA. Investigations into deviations included thorough review of causes of human error; there was an assessment of staff levels and workload on that day to assess influence of external factors on the ability of staff to perform routine activities.

Root cause analysis was thorough. The depth of investigations (noted in [redacted]) identified subtle differences in actual practice between analysts prompting changes to the workbooks used to drive consistency. A 3 part root cause code was assigned detailing the work area (e.g sterility) the item at fault (e.g. procedures) and the detailed reason (e.g. unclear/incomplete).

The error/incident rate was low. The facility performs ca 1300 tests per month (>15000 a year) and only [redacted] deviations and [redacted] non-conformances were raised.

Complaints:
No complaints had been raised since the previous inspection therefore no examples of the management process could be viewed.

Management review:
The most recent management review minutes were assessed. The level of detail recorded in caused of [redacted] and deviations was high and demonstrated a broad spread of root causes. Due to the low volume of errors made by the facility no meaningful conclusions could be drawn or trended at this time. One point to note is that although the CAPA completion rate was consistently around 60% per month only 3 CAPA's were overdue by greater than three weeks due. This was due to measures outside of the facility's control. Trending takes place quarterly and is reported via the quarterly management meetings.
Updates to regulatory requirements were documented and trained out by a consultant QP, [redacted]

Self-inspection
Procedures for self-inspection had recently been revised and had become confused in terms of terminology. The facility work with 2 QPs who provided conflicting opinions and the facility had, based on the reasons cited in the deficiency raised, opted to name them the wrong way around.

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The process described for self-inspection in [redacted] (titled internal audits) however was robust and review of activities performed the previous year demonstrated the audits undertaken were of good scope and depth and raised findings that added value. These audits were undertaken twice a year by an independent consultant QP, [redacted]) ensuring all areas defined by the SOP were covered each year.

Additional audits were described in [redacted] (titled self-inspection) that sought to evaluate compliance with SOPs via witness auditing, audit trailing and review with tests for review selected based on deviations/CAPA etc. General laboratory operations such as metrology were also covered. These audits were assigned randomly to staff across the unit and included within workload and were not intended to be truly independent.

C4 Document Control

Procedures were approved and issued as hardcopy documents, with a revision page to show reason for update, training requirements, revision history and documented control of copies. Copies of SOPs and test methods were available as hard copy within the laboratory and in the office.

The [redacted] system generates all testing worksheets from approved specifications and also subsequent Certificates of Analysis.

C5 Facilities and Equipment

The environmental monitoring records were reviewed for August 2018. The facility had followed their procedures for monitoring with the exception of the inclusion of an additional criterion for [redacted]. The additional criteria for [redacted] was for 3 consecutive readings above the alert level, but there were no defined actions to take in the event of this occurring.

The facility was well ordered and laid out. A shift system was in operation to maximise equipment usage. This was well planned.

The main laboratory and plate reading area was unclassified. All non-sterility testing was performed in safety cabinets with a limite of [redacted] applied for monitoring. Cleaning regimes in this area were in place and acceptable [redacted] and pre-sept rotated weekly and prepared daily for floors, [redacted] sterile [redacted] for surfaces). Media and plates are all purchased.
The following activities were observed: morphology, plate counts (EM and product, direct inoculation and membrane filtration) and sterility test reading.
Sterility testing was performed in an isolator maintained in a Grade D room with an appropriate anteroom. Mirrors and pictures were in place to aid gowning. The contact time and method for cleaning the Grade D room was questioned. Moistened wipes were used on a mop with a specified number of spray applied to the wipe. The inspector questioned whether the floow would remain wet for the contact time and the facility provided validation data to justify their method where this was specifically evaluated.

C6 Sample Handling and Control of Reagents (including Reference Substances)

Sample flow was evaluated but booking in procedures were not interrogated in depth.
Control of reference standards was not reviewed with the exception of viewing the storage location which was acceptable.

C7 Test Data, Preparation of Certificates of Analysis/Reports and Record Retention

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Testing

Some issues were identified with the methodology for sterility testing but these were not considered to impact upon the results obtained and were raised at "other" deficiency level only. The [redacted] level at the start of the sterility test was checked but no confirmation documented. In respect of the deficiency relating to revalidation of sterility test operators it is noted that aseptic practice was revalidated.

Data

Data were well ordered and easy to inspect. There were gaps relating to data integrity and the risk assessments in place were relatively weak. Due to the limited systems in place and relative risk these gaps were not deemed to pose a significant risk to the data generated and reported and were therefore raised as at "other" deficiency level. Further detail is given in section D.

Reporting

It was not explicit when unvalidated methods were used because only the word "unvalidated" appeared on the certificate of analysis (note: this was limited to a bulk excipient manufacturer)

C8 People

Initial regulatory training was provided internally on commencement of employment.
Regulatory refresher training was provided by [redacted] The content of the training delivered was good, did not rely upon repeat reiteration of previous sessions and had interactive aspects to stimulate thought and discussion and aid learning. The content was relevant and demonstrated an awareness of common issues e.g. a session included why human error shouldn't be a routine root cause.
Technical on the job training was comprehensive with detailed workpacks demonstrating training on methods.

Job descriptions and CVs were compliant and were reviewed for [redacted] and [redacted]
One conflict of interest relating to a dual role was raised.
The organogram is in appendix

C9 Contracts and agreements

Contracts were in place for the QPs involved in the facility's operation and that for [redacted] reviewed.
Service level agreements were in place with companies activities were outsourced to. These were reviewed without comment for [redacted] Deficiencies were raised for the contracts in place with [redacted].
Technical agreements in place with customers were reviewed for [redacted] without comment.

SECTION D DEFICIENCIES

1. CRITICAL

None

2. MAJOR

None

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3. OTHER

3.1 Corrective and preventative actions performed in response to deviations were not always adequate as evidenced by:

3.1.1 The preventative action to deviation [redacted]4 was to provide supplementary training to all analysts to remind them to immediately report method deviations to Helvic management. During this deviation is was noted that the trainer [redacted] had also failed to follow the procedure and there was no evidence to support his suitability to provide the retraining.

3.1.2 The root cause analysis of deviation [redacted] attributed the cause of the deviation to inconsistent data checking by analysts but there was no assessment of the procedures [redacted] to ensure sufficient guidance was included.

3.1.3 There was no requirement within company procedures to consider whether supplementary training delivered as part of corrective and preventative actions needed to be added into the main training package for that activity.

EU GMP Chapter 2 Principle, C1.4(xiv)

3.2 The validation of [redacted] in the bacterial endotoxin test conducted under validation [redacted] was not performed in accordance with the [redacted] "validation and routine testing of bacterial endotoxin test"). The SOP required the validation to be performed on 3 batches of product however only one was used in the validation.

EU GMP C1.8(v), C1.9(iii), A15.1.2

3.3 Contracts and agreements in place with service vendors were not always adequate as evidenced by:

3.3.1 The contract and agreement with [redacted]) dated February 2018 for the [redacted] system referred to Helvic as the contract acceptor, when they were the contract giver. In addition the contract stated that [redacted] would provide a data archiving process but the data was not subject to formal archive.

3.3.2 The service level agreement with [redacted] dated January 2016 did not include the requirement or timescale for [redacted] self storage to notify Helvic when an incident occurred that could impact upon the data stored within the facility.

EU GMP C4.10, C7.14, C7.15

3.4 The environmental trend data report for August 2018 included a definition of an out of trend [redacted] as three of more consecutive

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readings above the specified alert limit. Three consecutive readings were above the alert limit ([redacted] for the air monitoring of the clean room in August 2018 but there was no defined process on actions to be taken in the event of an [redacted]

EU GMP A1.20

3.5 The investigation report for Deviation [redacted] contained the following in section 5, Root Cause Analysis, page 4 of 6 "The sample type under test has a tendency to display turbidity that is not true growth and is caused by the product interacting with the media". This could not be substantiated during the inspection.

EU GMP C1.8(vii)

3.6 Procedures for sterility testing were deficient in that

3.6.1 The frequency of reading sterility tests was not adequate. The SOP required them to be read at intervals, as is also stated within the pharmacopoeial monograph. In reality several incidences were identified where tests were not read until day 13 or had significant gaps where they were not reviewed e.g. reading on Days 4, 13 and 14.

3.6.2 Confirmation that a check was conducted to ensure less than 1/3 of the media was [redacted] at the start of the test was not documented.

3.6.3 The sterility test was excluded from operator requalification procedures on the basis of running negative and positive controls within the test. This is not considered appropriate.

EU GMP A1.37
British Pharmacopoeia Appendix XVI A. Test for Sterility

3.7 Certificates of analysis issued to clients were not always adequately transparent as evidenced by:

3.7.1 During [redacted] investigation [redacted] retest results were reported separately from the original [redacted] result which had not been invalidated. Unless a result has been invalidated it must be reported with any retest results.

3.7.2 Where testing was performed to unvalidated methods certificates of analysis stated "unvalidated". It was not always clear this referred to an unvalidated testing method because for some testing (e.g. certificates [redacted] this was stated under a heading of "specification".

EU GMP C4.2

3.8 Procedures for self-inspection had recently been revised and were no longer appropriately named. [redacted] "self-inspection"

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	described operation checks to confirm that laboratory activities were performed in accordance with SOPs. This activity was not independent, did not appraise the effectiveness of the pharmaceutical quality system and was not therefore self-inspection as described by the EU GMP Guide. [redacted] the historical self-inspection SOP had been renamed "Internal Audit". This described an independent evaluation of the pharmaceutical quality system by an external consultant to ensure independence, on behalf of the company and is therefore self-inspection as described by Chapter 9 outsourced in accordance with Chapter 7.
EU GMP	C1.4(xvii), C9.2
3.9	Arrangements to assure data integrity were deficient in that:
3.9.1	Risk assessments lacked depth and did not adequately identify operational gaps and consequently control measures were not robust. For example, paper workbooks were not formally released and were open to being photocopied to create spare pages.
3.9.2	Paper print outs from electronic systems were considered raw data
3.9.3	There was a lack of knowledge on the data life cycle within systems. For example, the storage location of data within the temperature monitoring system was not known and had not been considered during risk assessment.
EU GMP	C4.1, C4.2, A11.1
3.10	Staff member [redacted] held a dual role undertaking some quality related tasks and some operational tasks. There was no documented assessment of the conflict of interests this creates and no formal mitigation/control methods in place.
EU GMP	C2.3
3.11	An electrical socket bank was present on the floor within the Grade D cleanroom which hindered effective cleaning of the floor.
EU GMP	A1.49

4. COMMENT

None

SECTION E INSPECTION OUTCOME & RECOMMENDATIONS

Date Post-Inspection Letter sent	30 October 2018
Facility response acceptable?	One RFI sent, acceptable response received 06 December 2018
Was supporting evidence provided?	None requested
Will a recommendation be made to the Licensing Office to support this laboratory being named on licences?	Yes
Highlight issue referred to other GXPs	None
Date request for GMP Certificate forwarded on sentinel	11 Dec 2018

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[redacted]

Appendix 2

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:	2
Other deficiencies this inspection:	11	Other deficiencies Last Inspection:	12

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(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	[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 – additional factors (✓applicable box)	
None relevant (default)	[redacted]
Significant concern over robustness of quality system to retain adequate control	
First Inspection	
Volume and or type of work	
Significant failures to complete actions to close deficiencies raised at the last inspection.	
Significant Changes reported in Change report	
Significant mitigating factors applied by the site	
Higher risk rating identified by other GxP and considered relevant to this GMP site	
Regulatory action related to the site	
Failure to submit update change reports of significant change or slippage in commitments from post inspection action plan.	
Other additional factor (record details and justify below)	

(d). Inspector's Supporting Information/ Justification Related to additional Factors
None

(e). Risk Rating Result Incorporating additional 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). Conclusions : Inspectors final comments on risk rating:
[redacted]

(g). Senior/ Expert	
Risk rating level	
Comments	
[redacted]	

(h). Confirm Agreed Risk rating following this inspection:			
Rating:	[redacted]		
Next Inspection due by and recommend number of days on site:			
Name:	[redacted]	**Date:**	11-Dec-2018

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Appendix 3

Update to Contract GMP QC Testing Laboratory Risk Assessment

Performed by: **Date:**

Revised Risk assessment no.

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[redacted]

Inspectors Supporting Information/ Justification Related to Discriminatory Factors

[redacted]

[redacted]