Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Clinigen Healthcare Ltd
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DE13 0BY

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine re-inspection

Licence or Reference Number: MS / WDA(H) 31644

Licence Holder/Applicant: Clinigen Healthcare Ltd

Details of Product(s)/ Clinical trials/Studies: QP certification of IMPs, importation of unlicensed medicines, wholesale dealing of licensed and unlicensed medicines.

Activities carried out by company:	Y/N
Manufacture of Active Ingredients	N
Manufacture of Finished Medicinal Products – Non sterile	N
Manufacture of Finished Medicinal Products - Sterile	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	N
Packaging - Secondary	N
Importing	Y
Laboratory Testing	N
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *Wholesale dealing*	Y

Name and Address of sites inspected (if different to cover): Clinigen Healthcare Ltd occupied two separate sites in the Burton-on-Trent area. This inspection covered Unit 2, Brunel Drive (MHRA site number 4487301) and Pitcairn House, Crown Square, First Avenue, Burton-on-Trent, Staffordshire DE14 2WW (MHRA site number 91930).

Site Contact: [redacted]

Date of Inspection: 1st August 2017

Lead Inspector: [redacted]

Case Folder References: GMP/GDP 31644/4487301-0008, GMP/GDP 31644/91930-0006

Section B General Introduction

B1 Background information

The Clinigen Group was formed from a merger of 3 companies:

- Clinigen Clinical Trial Services (formerly Keats Healthcare) – sourcing comparator products for clinical trials
- Clinigen GAP - Global Access Program for named patient supplies
- Clinigen Specialty Pharmaceuticals

In 2015 Clinigen acquired Idis and Link Healthcare, and in total the group employed approximately 500 people. In addition to the Burton-on-Trent headquarters, the company also had the former Idis site in Weybridge, and a number of overseas offices.

At the time of the inspection, the group was simplifying its structure and reducing the number of licenses. Clinigen Healthcare held MS 31644, WDA(H) 31644 and a small number of Marketing Authorisations, and these were unaffected by the proposed changes. Clinigen CTS held MS 20929, WDA(H) 20929 and MIA(IMP) 20929; the company had submitted termination applications for the MS and WDA(H), and would transfer MIA(IMP) to Clinigen Healthcare, so that all 3 remaining licences were under common ownership.

Previous Inspection Date: 19th Dec 2013

Previous Inspectors: [redacted]

B2 Inspected Areas

Introductions
Licence review
IMP activity and plans for licence transfer
Management of unlicensed products – TSE, import notifications
Wholesale transactions
Supplier verification, technical agreements, audits
Customer verification
Transport from 3rd country/temp monitoring/excursions
Management review
Change Control
Deviation and CAPA
Complaints
Recalls
PQRs for products where Clinigen is MA holder – API audits, supply chain
Returns, rejects
Distribution and shipment
Self-inspection

Warehouse facilities:

- Site security
- Temperature monitoring.
- Goods receipt (inspection, documentation checks), stock control
- Segregation (licensed/unlicensed or EEA/Export products)

Limitations / exclusions to inspected areas

None

B3 Key Personnel met/contacted during the inspection

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

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	v2, 13 July 2017	Y
Compliance Report	25 July 2017	Y
Comments: None		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes are recorded in the pre-inspection compliance reports held in the case folder.

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

Multiple staffing changes had occurred since the last inspection, including the QP, RP and Quality Director. There had also been some reorganisation of the business divisions.

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

The previously-advised new [redacted] system had been delayed due to the various company mergers and changes. A new [redacted] system for the whole group had been identified and was in the final design stage at the time of the inspection.

Expansion of the cold store capability was also planned.

C2 Action taken since the last inspection

Issues identified at the previous inspection had been addressed satisfactorily.

C3 Starting Materials

General

Suppliers were assessed and approved in accordance with [redacted] and [redacted] Names and addresses were verified and checked against the relevant UK/EU manufacturer/wholesaler authorisations and suitable references such as the EudraGMDP database or US FDA. Each supplier was subject to a risk assessment which determined whether a questionnaire and/or audit was required. Technical agreements were required for all approved suppliers. The MHRA monthly lists of suspended licences were regularly reviewed, along with EU Statements of Non-Compliance.

Compliance with TSE Guidelines

TSE statements were obtained as part of the initial supplier qualification process. However, for those products where Clinigen was the MA holder, there was no requirement for any periodic review thereafter. The TSE statement for [redacted] API from [redacted] was dated June 2010 and had never been updated.

API Compliance

The technical agreement with [redacted] for the supply of [redacted] stated that Clinigen were responsible for ensuring the GMP compliance of the API. The API was manufactured at [redacted] and an acceptable audit report was available.

C4 Pharmaceutical Quality System

The management review process was described in [redacted] which had been implemented in July 2017. A Quality Council had been established and was scheduled to meet every quarter. The company had revised its metrics and was now monitoring a range of KPIs including change controls, deviations, technical agreements, complaints, internal audits, returns and training adherence. The monthly metrics from 2017 indicated that the PQS was not in an effective state of control, as indicated by the consistently high percentage of overdues:

- Change controls at 60-90% overdue throughout 2017
- Deviations at 70-90% overdue
- Service-level complaints at 90% overdue
- Technical agreements at 40% overdue

It was evident that a contributory factor was a lack of resource. In addition to the numerous changes in quality-based staff, there were several vacancies in the quality group at the time of the inspection, and it appeared that the current staffing levels were unable to make a significant impact on the number of outstanding tasks. The minutes from the latest management review meeting recognised the issue; they had allocated some further resource to the Burton office, and had increased the frequency of review meetings to every 6 weeks.

The change control procedure was [redacted] and the system had been overhauled in March 2017. Consequently there were separate lists of changes under the current and previous systems. The updated process included an element of risk assessment, and contained provision for the approval of extensions to due dates. All changes were tracked on an [redacted] spreadsheet. Example records were seen including [redacted] (closure of the [redacted] program) and [redacted] ([redacted] related substance method updated as per Ph Eur). It was noted that change controls had been closed without full supporting evidence of the completion of all actions (as required by the SOP), for example [redacted] had been closed despite two of the five actions having no supporting evidence of completion.

In a similar manner to change control, the deviation procedure had been recently revised (May 2017) and there were two lists of deviations from the new and old systems. Examples reviewed included [redacted] (two shipments of [redacted] made prior to the program start) and [redacted] (a minor issue with the shipment address for a delivery of [redacted] It was evident that the assigned CAPA for [redacted] did not address the root cause, whereby a Program Manager had failed to follow procedures.

The latest PQR for [redacted] was reviewed. This covered [redacted] batches over the period Apr 2015 to Mar 2016. The report was produced by the manufacturer [redacted] and was suitably detailed. Clinigen provided an additional document review, signed by the QP and Quality Manager.

C5 Personnel

The Burton-on-Trent site employed approximately 100 people. The staff appeared knowledgeable about their roles. Training was combination of SOP reading, on-the-job training and an annual session on GDP and falsified medicines awareness. This included a written test which required an 80% pass mark.

C6 Premises and Equipment

The company's storage and distribution activities took place from Unit 2, Brunel Drive in Burton-on-Trent (MHRA site 4487301), located approximately 6 miles from the head office at Pitcairn House (site 91930). The building had secure access, security lighting and CCTV. There was a single roller door for handling all goods in and out; these activities were separated by time to prevent potential for mix-ups. The main part of the warehouse was controlled between 15-25°C, and there were [redacted] cold rooms at 2-8°C, each containing two chillers which switched over every 12 hours. There were also a large number of freezers used for conditioning and storage of freezer packs for cold-chain transportation. There were locked cages for quarantined goods, returns and potential falsified product, and a locked CD store. It was noted that the quarantined cage was very full, including some items that had been present for some time.

Continuous temperature monitoring was in place, with a total of 23 probes around the facility and 2 in each cold store. Audible alarms and auto alerts were triggered in the event of an excursion. A review of recent monitoring data did not indicate any excursions or issues. Mapping studies were performed every 12 months.

Goods receipt checks were evident, and the associated records were suitably detailed. Photographs were taken from every delivery to aid in the identification of damaged goods or potentially falsified products. Batch numbers and expiry dates were recorded. All delivery paperwork was also scanned and stored on a shared drive. The warehouse location, status and quantity of a batch of [redacted] was challenged on the [redacted] computer system, with no issues evident.

C7 Documentation

The importation of unlicensed medicines was described in [redacted]. The SOP referred to MHRA Guidance Note 14 and the unlicensed TSE requirements, though it had not been reviewed or revised since Jan 2013. Consequently it did not reflect the current personnel on site. It also contained out of date lists of EU MRA countries and PIC/s members. GN14 had been revised in 2015 but there was no documented assessment or gap analysis of Clinigen operations against the new guidance.

Importation requests were documented on a form [redacted] and tracked on a spreadsheet [redacted] Examples of import transactions were inspected, including [redacted] imported from Sweden due to restricted supply of the licensed product) and [redacted] No issues were noted.

Documentation for various wholesale orders was reviewed. This included [redacted] (sourcing goods from [redacted] for supply to [redacted]), and two orders for German and Austrian pharmacies. No issues were noted.

C8 Production

Not applicable.

C9 Quality Control

Not applicable.

C10 Outsourced Activities

Clinigen held a tracking log for all current technical agreements. The agreement with [redacted] for the provision of periodic clinical supplies was inspected, and was suitably detailed including sections on temperature/transportation requirements, recalls and potential falsified products. The agreement was dated Aug 2013 and was overdue for review; however no transactions with [redacted] had taken place since June 2015 when [redacted] was supplied via [redacted]

The 2017 supplier audit schedule was inspected. The audit report for [redacted] was provided by a third party auditor on behalf of Clinigen. A contract between Clinigen and the auditor was in place, and a detailed CV had been provided.

C11 Complaints and Product Recall

A significant proportion of complaints were in relation to temperature excursions. Examples were reviewed including [redacted] and [redacted] It was evident that all associated records connected with the complaints were not fully captured in the complaint documentation. For example, [redacted] had been opened but there were no further entries in the subsequent six weeks up to the date of the inspection. the investigation had not been completed, and there was no evidence of any correspondence with the complainant. In addition, there was no evidence that the company had considered previous complaints to determine whether there was a recurring issue.

There had been no recalls in the last three years. The recall procedure [redacted] was suitably detailed. A mock recall had been performed in Feb 2017, mimicking a Class I recall of [redacted] the recall process was manual in nature but was complete successfully within 24 hours with a full reconciliation achieved.

C12 Self Inspection

A self-inspection program was in place. This was in the process of being revised to include a review of existing transportation risk assessments.

C13 Distribution and shipment (including WDA activities if relevant)

Customer verification was described in [redacted] New customers (and their site addresses) were verified against copies of their wholesale authorisation, pharmacy registration or hospital operating licence.

Pick orders were generated by the customer services department, and the orders were then picked and packed by two warehouse operators, who checked each other's work.

Transportation was outsourced to various couriers, including [redacted] Technical agreements were in place, and the couriers were all included on the approved supplier list.

The company also held an API registration, as they distributed [redacted] APIs for use in products where Clinigen were the MA holder. All the APIs were manufactured in Europe, purchased by Clinigen and held in the warehouse at Unit [redacted]

C14 Questions raised by the Assessors in relation to the assessment of a marketing authorisation

None

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

D1 Critical

None

D2 Major

2.1 The Pharmaceutical Quality System (PQS) was deficient, as evidenced by:

2.1.1 The PQS was not in an effective state of control, as indicated by the monthly KPI metrics. For example but not limited to:

2.1.1.1 Change controls were consistently between 60-90% overdue during Jan-July 2017.
2.1.1.2 Deviations were between 70-90% overdue throughout Jan-July 2017.
2.1.1.3 Service-level complaints were consistently at 90% overdue in Jan-July 2017.
2.1.1.4 Overdue technical agreements were at 40%.

2.1.2 The PQS was not adequately resourced, in that the quality headcount had several vacancies, and the current staffing level was not able to significantly improve the metrics listed above.

2.1.3 Change control records were not supported by adequate evidence for the completion of all actions, for example [redacted] which had been closed despite two of the five actions having no supporting evidence of completion. This was also contrary to the requirements of the change control procedure [redacted]

2.1.4 Deviations and CAPA were inadequate, for example [redacted] which did not appear to address the root cause of a Program Manager failing to follow procedures relating to the supply of [redacted] before the program launch.

2.1.5 Complaints were not fully documented, for example [redacted] relating to a temperature excursion of the cold chain product [redacted] in June 2017, in that:

2.1.5.1 There were no further entries associated with this complaint in the six weeks following the initial details on the complaint form which was raised on 15 June 2017.
2.1.5.2 The required investigation, due in mid-July, had not been completed at the time of the inspection.
2.1.5.3 There was no documented evidence of any correspondence with the complainant.
2.1.5.4 There was no documented consideration of previous complaints to determine whether there was a recurring issue. The inspector noted that the majority of complaints were for temperature excursions.

Reference: EU GMP 1.4 (viii, xiv), 1.5, 1.8 (v, vii, xi), 4.8, 4.29, 8.2, 8.5, 8.12
Reference: EU GDP 1.2, 4.2, 6.1

D3 Others

3.1 Procedures for the control of unlicensed medicines were inadequate, as evidenced by:

3.1.1 Procedure [redacted] was out of date in that it had not been revised since Jan 2013, and did not reflect current Clinigen personnel.

3.1.2 The lists of EU MRA countries and PIC/S members in [redacted] were not current.

3.1.3 There was no documented gap analysis of Clinigen operations related to unlicensed medicines following the 2015 revision to MHRA Guidance Note 14.

Reference: EU GMP 4.5
MHRA Guidance Note GN14

3.2 TSE controls were inadequate, in that TSE statements for those products where Clinigen was the MA holder were not subject to periodic review. For example, the TSE statement for [redacted] API from [redacted] was dated June 2010.

Reference: EU GMP 5.27
EMA Note for Guidance on minimising the risk of TSE EMA/410/01 v3

D4 Comments

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	✓	[redacted]	
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The closing meeting was held with the company and the deficiencies were accepted in a positive manner. The company committed to providing a response within the specified timeline.

F2 Assessment of responses to inspection report

An initial response was received on 29 Aug 2017. A further response was provided on 22 Sep 2017 which was accepted by the inspector.

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	✓
GMP as required by HMR 2012 (as amended)	✓
Directive 2001/20/EC	N/A
Directive 2001/82/EC	N/A
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	✓

and is acceptable for the products in question.

Name and Dated Signature of Inspector:

Signed: [redacted] **Dated:** 22 Sept 2017
Name [redacted]

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	1	Last inspection:	0
Other deficiencies this inspection:	2	Last Inspection:	3

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

Risk rating level	Input from current Inspection Findings (last inspection findings applicable to rating V only)	Provisional rating – this assessment	Final rating last assessment
0	Serious triggers outside the inspection cycle	[redacted]	
I	Critical finding		
II	>/= 6 Major findings		
III	<6 Major findings		
IV	No critical or Major findings		
V	No critical or Major findings from current or previous inspection and <6 other findings on each.		

(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 recalls, notifications to DMRC or rapid alerts since last inspection
	Nature of batch specific variations submitted since the last inspection give concern over the level of control
	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 counter-signature for RR II)
	Other discriminatory factor (record details and justify below)

(d). Inspectors Comments Related to Discriminatory Factors

[redacted]

(e). Risk Rating Result Incorporating Discriminatory factors (✓ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

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

[redacted]

(g). GMP or GDP certificate conditioning remarks required as a result of risk-based decisions noted in section (f) above

[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:

[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 gmpinspectorate@mhra.gsi.gov.uk