Medicines & Healthcare products Regulatory Agency

MHRA

INSPECTION REPORT

INTRAPHARM LABORATORIES LIMITED

THE GRANARY

THE COURTYARD BARNS

CHOKE LANE, COOKHAM DEAN

MAIDENHEAD

and

PECKFORTON PHARMACEUTICALS LIMITED

CREWE HALL

CREWE

CHESHIRE

CW1 6UL

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA/WDA(H) 17509
MIA/WDA(H) 15760

Licence Holder/Applicant: Intrapharm Laboratories Limited (17509)
Peckforton Pharmaceuticals Limited (15760)

Details of Product(s)/ Clinical trials/Studies:

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 distribution, unlicensed medicinal products*	Y

Name and Address of site(s) inspected (if different to cover):

Site Contact: [redacted]

Note: Following this inspection, there was a subsequent assessment in Nov 2022 of variation WDA(H) 17509/M-0025 for the nomination of a new RP and RPi (Insp GDP 17509/4751678-0011). This assessment is more recent and will include more recent contact information for the company.

Date(s) of Inspection: 16/12/2020

Lead Inspector: [redacted]

Accompanying Inspector(s):

Case Folder References: Insp GMP/GDP 17509/4751678-0010

Section B General Introduction

B1 Background information

The organisation was in the process of significant change at the time of this inspection. The inspection was performed remotely during Covid restrictions.

Intrapharm was originally founded in 1999 and was acquired by Abbey Pharma in April 2009. Peckforton was founded in 1995 and acquired by Abbey Pharma in 2014. The Abbey Pharma group was acquired by Riemser Pharma (Germany) in November 2015. Intrapharm and Peckforton operate a conventional 'virtual importer' setup with all manufacturing, storage and testing outsourced to third parties. Following the acquisition of Peckforton, a programme to harmonise the quality systems had been performed. The company had previously been using the Crewe site for limited batch release activities whilst details on MAs of the batch release sites were updated.

Following this inspection, the Peckforton Pharmaceuticals Limited MIA 15760 and WDA(H) 15760 was subsequently terminated in April 2021 and it was understood that the site at Crewe Hall (Site ID: 7060) was closed and no longer used for GMP or GDP activities with records associated with Peckforton being stored c/o Intrapharm Laboratories Limited site at Cookham Dean (Site ID: 4751678). Considering the site closure/licence termination, certificates were not issued for the site at Crewe Hall.

In February 2020, Riemser Group were acquired by Esteve, a Spanish company. In November 2021 the company changed its name from Intrapharm Laboratories Limited to Esteve Pharmaceuticals Ltd.

It was identified that this inspection case had not been closed and for completeness this report has been issued and the certificate issued to reflect the December 2020 inspection.

Previous Inspection Date(s): 21 & 22 March 2017 (Cookham Dean, Maidenhead)
28 March 2017 (Crewe)

Previous Inspectors: [redacted]

B2 Inspected Areas

The quality system was inspected, including:
Management review, deviation investigations, CAPA, Artwork control, Product Quality Reviews, Training, Outsourced activities, Control of starting materials (vendor management, excipient risk assessment, elemental impurities, API supply chain), Complaints, Recall, Arrangements for sampling, Stability data review, Distribution, Self-inspection

Limitations / exclusions to inspected areas

It was understood that there will be significant changes to senior management and significant changes planned to the quality management system that were not in place at the time of this inspection. Therefore, the future organisation was not inspected.

Change control was not inspected in detail on this occasion and may be of interest at a future inspection.

The company had not completed the transfer of MAs to reflect the change of batch release site (i.e. removing [redacted] at the time of this inspection. Verifying completion of this activity may be of interest at a future inspection.

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]		

* Attended closing meeting

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted]	Y
Compliance Report	Dated 11 Dec 2020 and approved 13 Dec 2020	Y
Comments:		

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:

[redacted]

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

It was described that there would be significant changes to senior management and significant changes were anticipated to the quality management system.

C2 Action taken since the last inspection

Refer to pre-inspection compliance report held in the case folder.

Although previous findings had generally been addressed, a deficiency was raised, see D 2.3.2 of this report.

C3 Starting Materials

General

[redacted] effective 30 Nov 2020 described [redacted] A copy of the list of approved suppliers was provided that included contractors, QC labs, API manufacturers and FP manufacturers with scope of activities described.

A copy of supplier audits from 2019 and 2020 were reviewed.

An example ([redacted] Quality Risk Assessment of elemental impurities was reviewed describing how ICH Q3D had been applied and the excipient risk assessment for the same product.

Deficiencies were raised, refer to Section D 3.2 and D 3.3 of this report.

Compliance with TSE Guidelines

Management of TSE risk was covered by [redacted] Issue No. 03 Compliance with Transmissible Spongiform Encephalopathy Guideline. Each product manufacturer was required to produce a statement indicating that the product was either free of TSE risk (no animal origin materials used) or that any animal origin materials were identified and were complaint with EMEA/410/01. Declarations were valid for two years from date of receipt.

API Compliance

A deficiency was raised associated with a API supply chain flow chart, refer to Section D 3.1 of this report.

C4 Pharmaceutical Quality System

The site described that it was anticipated that the quality management system would be significantly changed, but this was being developed at the time of this inspection and was not inspected.

<u>Management Review</u>

The requirements for management review were captured in [redacted] Issue No. 03 Quality Management Review. Meetings were to be held on a quarterly frequency, led by the Quality and Manufacturing Director and involving Senior Management, the Technical Affairs Director and the Purchasing & Commercial Manager. A standard meeting agenda was used. No management review meetings had been held since May 2020. Concerns were also noted in terms of inadequate senior management oversight of Quality matters, particularly continuity of QP certification and a deficiency was recorded, see Section D.

Deviation investigation/CAPA

Deviations were managed according to [redacted] Issue No. 08 Handling of Quality Issues: Deviations, Out of Specifications Results, Abnormal Events, Out of Trend and Out of Expectation Results. At the time of the inspection a paper-based system was in place however replacement with Trackwise during 2021 was anticipated. The records for twelve deviation investigations were reviewed and a deficiency was recorded, see Section D. CAPA requirements were covered in the abovementioned SOP.

Artwork Control

Artwork was controlled following [redacted]

Change Control

A list of change controls for both Intrapharm and Peckforton were provided from 2017 to Dec 2020. Change control was not inspected in detail on this occasion and may be of interest at a future inspection.

Product Quality Reviews

A list of PQR reports from 2018 and 2019 was reviewed and examples inspected that included [redacted] Some of the examples selected indicated that the product had not been manufactured during the review period.

C5 Personnel

Both companies were supported by a shared group of seven UK-based staff. During the opening meeting for the office-based inspection the inspectors were informed of significant changes at senior level including the recent departures of the CEO and the Technical Affairs Director. Of concern, the Quality and Manufacturing Director/QP/RP also advised that he would be leaving the company in mid-February, with no other QP or RP named on the MIA or WDA(H) or variations submitted to MHRA to name replacements. A deficiency was recorded, see Section D.

Training was handled per [redacted] Individual hard copy training files were held by all employees to record induction, GMP, SOP and other types of training. GMP and pharmacovigilance refresher training was to be performed annually.

C6 Premises and Equipment

Remote inspection performed during COVID-19 travel restrictions, however physical inspection of facilities and equipment was not required due to the nature of the operations performed. The company operated under a virtual business model with all storage, manufacture and testing services contracted out to third parties under various Quality/Technical Agreements (QTAs) – see Section C10.

C7 Documentation

During the opening meeting for the office-based inspection the inspectors were informed of significant changes being planned to the company's quality and document management systems, with replacement of the current paper-based systems with electronic solutions starting in early 2021.

C8 Production

All products were manufactured and packaged by approved third parties.

The site provided a list of batches certified since the last inspection. Examples were selected to demonstrate how the QP batch certification procedure performed.

[redacted]

C9 Quality Control

No quality control activities were performed on site.

The site provided lists of OOS investigations and the inspector selected examples of these that were reviewed as part of the inspection.

A deficiency was raised, refer to Section D 2.1.1 of this report.

[redacted] would sample received product in the UK from the contract manufacturing sites in third countries.

A deficiency was raised, refer to Section D 2.2 of this report.

C10 Outsourced Activities

The procedure for Technical Agreements was [redacted] effective 30 Nov 2020.

The site provided a list of technical agreements and the inspector selected examples of these that were reviewed as part of the inspection.

The company would either audit sites themselves or use third party auditors on their behalf.

C11 Complaints and Product Recall

The site provided lists of complaint investigations and the inspector selected examples of these that were reviewed as part of the inspection.

The procedure for [redacted] effective 09 Dec 2019.

A deficiency was raised, refer to Section D of this report.

Recall was managed per [redacted] A dummy recall was required to be performed every twelve months in the absence of a true recall being necessitated. Four product recalls had been actioned since the previous inspection.

C12 Self Inspection

This subject was covered in [redacted] An annual self-inspection programme was set at the beginning of each year, focussing on output from quality management reviews.

C13 Distribution and shipment (including WDA activities if relevant)

A deficiency was raised, refer to Section D 2.1.2 of this report.

Following this inspection, there was a subsequent assessment in Nov 2022 of variation WDA(H) 17509/M-0025 for the nomination of a new RP and RPi (Insp GDP 17509/4751678-0011). This assessment is more recent and will include more recent contact information at the company.

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	Investigations were deficient in that:
2.1.1	The review of OOS investigations was inadequate when more information came to light, as evidenced by [redacted] that described a 12 month stability OOS for lyophilized product batch [redacted] of 5.1% moisture against the specification of NMT 4.5% and was higher than previous data investigated. It was not considered that although DMRC had previously been informed, that an update should have been provided with this new information that was higher than previous data and to assess if previous product impact assessments would remain valid.
2.1.2	Events with potential product impact were not always being investigated in the quality system to identify appropriate corrective actions and/or preventative actions, as evidenced by risk assessment [redacted]) describing that 122 batches of [redacted] product transported in 27 shipments to the UK experienced temperatures of up to 34C for up to 38hrs and that the excursions could be tolerated on the basis of available stability data, therefore no corrective action was necessary with no future excursions up to 34C for up to 38hrs requiring investigations to be performed. It is acknowledged that the site no longer handles this product and has indicated that this practice would not be used in future.
2.1.3	There was inadequate documented assessment in complaint investigations as to whether a complaint could indicate a potentially falsified medicine, for example there were 3 complaints associated with [redacted] and it was described that it was not known how the customer had received the product.
EU GMP	C1.4(xiv), C1.8(ix), C1.8(xi), C6.35
2.2	Product quality reviews were deficient in that:

2.2.1 Stability data was described as a high-level summary without trended data being included as evidenced by [redacted] PQRs for 2018 and 2019.

2.2.2 Not all relevant data for a product was described, for example in [redacted] although some OOSs were referenced associated with stability data, [redacted] that was also relevant was not included in section 8.

2.2.3 The conclusion of [redacted] stated that the "Stability study of the product found stable and corresponds to the specification" was incorrect as stability moisture data was out of specification.

2.2.4 There was no trending of CMO finished product QC data and EU test lab data to compare data over time to identify potential differences and no procedure to describe how reviews would be performed.

EU GMP C1.10(vii), C1.11, C4.2, C6.9

2.3 Management oversight of GMDP activities was inadequate in that:

2.3.1 At the time of inspection, a Quality Management Review meeting had not been held since May 2020 and therefore did not comply with procedure [redacted] that described that these would be held quarterly. In addition, it was discussed at the time of inspection that the company was experiencing significant changes in personnel.

2.3.2 Commitments from the previous inspection (deficiency 2.1.1 from March 2017) were incomplete at the time of this inspection over 3 years later in that although systems had been established for excipient risk assessments, it was understood that these had not been completed for all products. The previous inspector had not been informed of this delay.

2.3.3 There was inadequate evidence of senior management involvement to ensure that the Pharmaceutical Quality System remained adequately resourced in that at the time of inspection it was described that the QP was leaving the company in February 2021 however that a replacement had not yet been employed that potentially could lead to inadequate training, knowledge transfer and considering that a licence variation would also be required.

EU GMP C1.5, C1.8(v), C2.1, C5.29

D3 Others

3.1 The supply chain flow chart provided for [redacted] did not fully describe the supply chain of API, in that: Starting materials for the active substance were not described, it did not describe what was the approved transport for the API and the conditions when it was transported from [redacted]

EU GMP C5.29

3.2 Actions required to provide assurance that elemental impurities were controlled within acceptable limits were deficient in that they were not being progressed in a timely manner, as evidenced by:

3.2.1	Quality risk assessment of elemental impurities [redacted] from Feb 2018 had not been approved at the time of inspection over 2 years later.
3.2.2	The action in the above assessment for 3 batches of finished product to be analysed for presence of elemental impurities by the end of April 2018 with subsequent revision of the risk assessment had not been done at the time of inspection.
EU GMP	C1.4(viii), C5.18
3.3	[redacted] excipient risk assessment was ambiguous in that the summary (page 1) described the manufacturer of [redacted] whilst page 20 that had the detailed assessment described this as a [redacted] in the UK.
EU GMP	C4.2
3.4	Rejected batches were not adequately recorded in the quality system in that:
3.4.1	The decision to reject [redacted] had not been recorded in the Quality Management System and was described as due to ongoing discussions over determining responsibility for the cost of this. This was not an appropriate reason for delaying recording the batch status.
3.4.2	The investigation for deviation [redacted] was ambiguous in that it did not record the decision to destroy the batch.
EU GMP	C1.4(viii), C4.8

D4 Comments

4.1 It was discussed that the next inspection may be sooner considering that there will be significant changes to senior management and significant changes are planned to the quality management system.

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]	[redacted]
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The closing meeting was held with the individual identified in Section B3 of this report and the deficiencies were verbally accepted in a positive manner. The company committed to addressing the issues.

F2 Assessment of response(s) to inspection report

An RFI was sent 03 Feb 2021 with response received 12 Feb 2021 that was accepted.

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
GMP as required by the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	✓
The Medicines for Human Use (Clinical Trials) Regulations 2004	
Regulation 5 of the current Veterinary Medicines Regulations	
Regulation C17 of the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	✓

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted]

Date: 01/03/2023

Accompanying Inspector: [redacted]

Inspection was performed during Covid pandemic. Report was not issued at time due to inspector availability, when resources were available and this was identified, the report was subsequently issued for completeness and associated GMP certificate issued.

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	3	Last inspection:	1
Other deficiencies this inspection:	4	Last Inspection:	4

(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		
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)

	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

The site has described planning significant changes to QMS and changes to senior positions. It may be of interest to arrange an inspection when these changes have been performed.

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

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	
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

N/A

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

GMP Certificate:
None

GDP Certificate:
None

(h). Conclusions

Inspectors comments on risk rating:

24 months is an appropriate reinspection frequency.

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

~~**Expert / Operations Manager / CMT**~~ **(delete as appropriate)**
Risk Rating: III
Comments:
None

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

Risk Rating:	Next Inspection target date:
III	**Dec 2022**

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.gov.uk