Medicines & Healthcare products
Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

AbbVie Ltd
AbbVie House,
Vanwall Business Park,
Vanwall Road,
Maidenhead,
Berkshire
SL6 4UB

Head Office:
Inspection, Enforcement & Standards Division, MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

Telephone: 020 3080 6000
Email: info@mhra.gov.uk

Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA(IMP)/ WDA (H) 41042

Licence Holder/Applicant: AbbVie

Details of Product(s)/ Clinical trials/Studies: Supply of clinical trial products across a range of therapeutic areas including neuroscience, oncology, virology, gastroenterology and eye care.

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: *Importer of IMPs from EU* Wholesaler	

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

Site Contact: UK MIA (IMP) [redacted]

WDA [redacted]

Date(s) of Inspection: 21 September 2023

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp IMP 41042/12696367-0007, Insp GDP 41042/12696367-0008

Section B General Introduction

B1 Background information

Abbvie UK Ltd operate as a virtual importer of IMPs that are manufactured in [redacted] which are supplied directly to GB clinical trial sites under a 2-step oversight process. The company also operates as a commercial distribution where products are imported into the UK from a distribution hub in [redacted] under the WDA(H). The company exports to [redacted] and have submitted a variation on the WDA(H) to add export to the licenced activities. The company integrated with Allergan on 01 April 2022

Previous Inspection Date(s): 19th November 2021

Previous Inspectors: [redacted]

B2 Inspected Areas

Deviations
Change controls
Management Review
QP Oversight
Complaints and Recalls
Outsourced Activities
Distribution and Shipment

Limitations / exclusions to inspected areas

Self-inspections

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]	[redacted]	[redacted]
[redacted]	[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	[redacted] 21 July 2022	N
Compliance Report	7th & 11th September 2023	Y
Comments: *the site master file did not contain all relevant sections as described in Part III		

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. Since the previous inspection there was completion of integration of AbbVie Ltd and Allergan Ltd to form a single entity as AbbVie Ltd.

Implementation of RPi
Change in EP/RPi
Integration of Abbvie and Allergan
[redacted]
Complaints process moved from post market quality assurance

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

Addition of ATMP: [redacted]

- AbbVie performs QP release
- A third party manufacturer is responsible for manufacturing, packaging and labelling
- No UK clinical trials involving [redacted] have yet been initiated

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

None

C2 Action taken since the last inspection

All actions appeared to have been addressed.

C3 Starting Materials

General

N/A

Compliance with TSE Guidelines

N/A

API Compliance

N/A

C4 Pharmaceutical Quality System

The pharmaceutical quality systems was managed globally

Deviations / Exception reports

Exception reports (ERs) were governed by [redacted] effective 23 Apr 2022. Exceptions were categorised into low, medium, and high severity and an impact assessment required. The process detailed requirement of root cause analysis to be performed using various root cause analysis tools. Timelines were defined that ERs and associated CAPA had to be approved within 90 calendar days which was not commensurate with the level of severity / risk. The SOP was silent in terms of recall requirements or notifying the relevant competent authorities and was silent in terms of notifying the QPs in the event of a high-risk ER. The SOP allowed 7 days to raise an ER.

In addition, [redacted] effective 16 Nov 2022 was presented during the inspection. This required ERs to be generated within 1 business day of discovery, and justification if not completed within 30 days. It was not clear during the inspection which SOP took precedence, and both were deemed to be excessive in length.

The following ERs were reviewed without comment:

[redacted] vials with lot numbers on crimp cap – "contains unblinding information". Study numbers [redacted] Date discovered 05 May 2023. During packaging of blinded lot [redacted] personnel noticed on 5 May 23 that the booklet label. Batches were destroyed and not shipped to the UK.

[redacted] WDA deviation regarding shipment to [redacted] without export licence. Initiated 26 June 2023, approved 04 July 2023. Investigation and CAPAs captured as child records of the parent exception record. Each child individually and independently approved. Risk assessment completed, and CAPA raised to amend the licence through change control process, pending MHRA approval of variation.

Change control

Change controls were governed by [redacted] effective 10-Feb-2023. Effectiveness checks were required by the procedure, and justifications needed if not performed. Implementation actions were raised in [redacted] these were then initiated once the parent record was approved for implementation. The following change control was reviewed during the inspection without comment:

[redacted] Raised 27 Jun 2023 Change approved for implementation on 4 Aug 2023. Change documented the risk assessment, action to submit the variation, and to update the GDP SOP with the requirements for the export licence once completed (SOP approved, pending being made effective). The final action to confirm variation approval was still pending as awaiting MHRA response.

Management Review

The Management review for Q1 2023 and Q2 2023 were reviewed (12 June 2023 and 07 September 2023 respectively). Attended by [redacted] Review covered Significant Events, Exception records, Complaints, Quality Metrics, Quality Plans & Changes, Regulatory Updates, Inspections & Audits. Minutes approved by all attendees. It was noted by the inspector that ERs were were reported against timelines based on 1 day for initiation, but 90 days for completion. See Deviations / Exceptions Records above.

QP Oversight process

UK R&D Oversight for Import of Investigational Medicinal Products to Great Britain was governed by [redacted] (Global effective 01 Jan 2022) and [redacted] effective (03 Dev 2021). The process included a 2-step process was described in the opening meeting and summarised below:

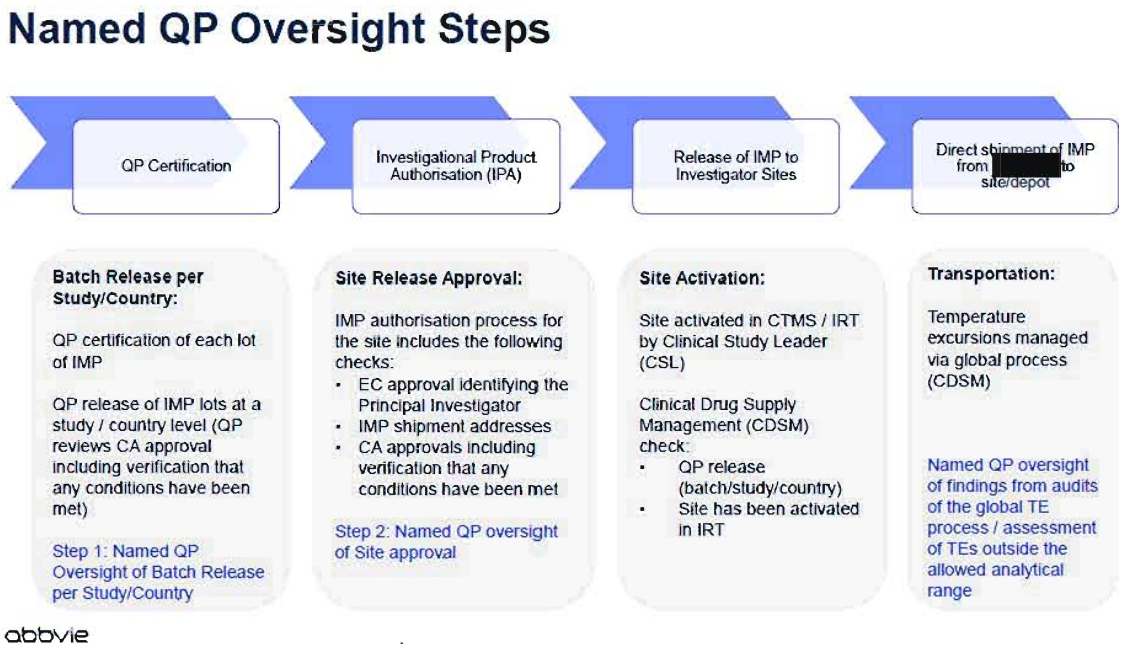

*figure taken from opening meeting

The QP oversight process for Study Number [redacted] Batch number [redacted] was reviewed without comment. [redacted] acted as the Sponsor. The QP was had oversight of the approved CTA and post approval commitments, ethics approvals for each clinical site, supply chain maps, product specification file and temperature excursions. The QPs named on the UK MIA(IMP) were the same QPs named on the [redacted] MIA(IMP), therefore it was the same QP responsible for certification of IMP in [redacted] and the UK QP oversight process. Transport, including temperature excursions were tracked and assessed globally via [redacted] by the [redacted] and was governed by [redacted] It was noted that the QP oversight process and verification occurred before transport of the IMP to the GB clinical site. Temperature excursions were required to be reviewed by the QPs prior to releasing the IMP for use on the IRT. The global IRT managed expiry dates for kits. Comparators were bought by the wholesale business, comparators underwent re-packaging in [redacted] and were subject to the same 2 step QP oversight process. Blinding requirements were documented on the IMP certification certificates.

New Product Introduction

New product introduction was not reviewed during the inspection and may be of interest at the next inspection.

C5 Personnel

QPs were based in [redacted] and were responsible for IMP certification in [redacted] and the IMP QP oversight process in the UK.

Training was not reviewed during this inspection.

C6 Premises and Equipment

N/A

C7 Documentation

AbbVie Ltd operated from a Global system with Global and local SOPs. A deficiency was raised as many of the SOPs reviewed were of significant length and there were examples where SOPs were difficult to follow with multiple references back to other documents.

It was noted that documents pertaining to the UK MIA(IMP) were slow in being made available to the inspectors.

C8 Production

IMPs were manufactured, certified and released in [redacted] They were imported into the UK via road and were subject to the UK Oversight process.

C9 Quality Control

N/A

C10 Outsourced Activities

Technical Agreements

The Internal Technical Quality Agreement between AbbVie Ltd (UK MIA(IMP) Holder) and the Clinical Trial Sponsor was reviewed. The Technical agreement did not detail responsibilities for transport, generation and management of IMPD, final QP certification, recall, disposal of IMP. An addendum QTA with [redacted] the transport provider was reviewed without comment.

The Internal Quality Technical Agreement between AbbVie UK and [redacted] effective 14 Sep 2023 was reviewed without comment.

C11 Complaints and Product Recall

Complaints were managed via the AbbVie global system.

C12 Self Inspection

Self inspection was not reviewed during the inspection and may be of interest at the next inspection.

C13 Distribution and shipment (including WDA activities if relevant)

Clinical supplies were shipped by the [redacted] unit directly to the clinical sites. For non-AbbVie sponsored studies, clinical supplies were allowed to be shipped to clinical sites directly or Great Britain Distribution Hubs and was subject to QP oversight process.

Wholesale Activities

Good Distribution Practice within AbbVie UK was governed by [redacted] The procedure detailed receipt at [redacted] who was responsible for supplier approval, storage, returns, and processing a breach of GDP. The 3rd part contract distribution hub, [redacted] provided a goods inbound checklist and shipping documentation to Abbvie UK to the RP/RPi. Th RP/RPi completed a checklist for local market release and sent confirmation to Abbvie Customers services and [redacted] and warehouse to highlight batches that have been released for distribution. The SOP also listed requirements for the RP and RPi. It was

described during the inspection that purchase order sales and numbers are trended and reviewed, although this was not described in the GDP procedure.

The company exported products to [redacted] only and had submitted a variation to the WDA to add this to the licence at the time of the inspection. Export was detailed in [redacted] and was reviewed, it was pending release following approval of the variation.

The RPi process was governed by [redacted] The RPi process for [redacted] batch [redacted] was reviewed during the inspection. RPi Checks included review of the CoA from manufacturer, QP release, shipping documents, temperature excursions, and a check on decommissioned status. Released on [redacted] was interfaced with the ERP system at the storage and distribution hub [redacted] Temperature excursions were managed via the [redacted] system, an impact assessment was performed and trended via the global team.

WDA UK Quality Defect and product Recall Process

Governed by [redacted] It detailed the different classifications of recall, there was no requirement to perform mock recalls out of hours. Mock Recall (GDP) initiated on 28th November 2022 for [redacted] and was reviewed without comment.

Customer Approval

Customer approval was governed by [redacted] effective 31 Dec 21 and reviewed without comment. The process required an annual licence check and a monthly check of terminated and revoked licences. It was noted that the SOP required review of EUDRAGMP website rather than the MHRA portal.

Transportation in the UK was managed via [redacted] A QTA was in place [redacted] 07/09/2023. [redacted] was approved via audit by the Global auditing team and shadowed by AbbVie UK RP, it was reviewed without comment.

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

None

D3 Others

2.1 **Outsourced activities were deficient as evidenced by;**

2.1.1 There was a failure to clearly define responsibilities for different steps within technical agreements. The internal technical quality agreement between AbbVie Ltd and [redacted] and [redacted] did not describe clearly who undertook responsibility for transport, generation and management for the IMPD, final QP certification, recall and disposal of IMPs.

Reference: EU GMP C7.15

2.2 **GDP Operations were deficient as evidenced by;**

2.2.1 The effectiveness of product recalls could not be assured, as there was no procedural requirement to perform mock recalls out of hours.

2.2.2 There was a failure to review sales of products to determine and investigate unusual trends or activities, as there was no documented procedure describing this process.

2.2.3 The Customer approval SOP, [redacted] effective 31 Dec 21 detailed review of Customer licences through the EUDRAGMP portal but was silent in referencing the MHRA portal.

Reference: EU GDP 5.3, 6.5

2.3 **The Pharmaceutical Quality System was deficient as evidenced by:**

2.3.1 Quality risk management processes were not being utilised in the management of exception reports (deviations). The SOP for exception reports [redacted] effective 23 Apr 2022) described that all exception reports and CAPA were required to be approved within 90 calendar days irrespective of the risk/impact of the issue. It was not explicit within global SOPs what level of effort, formality and documentation was required for high, medium and low severity reports.

2.3.2 There was a failure to use procedures that are unambiguous and easy to check as evidenced by:

2.3.2.1 Exception Reporting/Impact Assessment procedure [redacted] stated Exception Records must be raised within 7 calendar days of discovery (page 6) and completed within 90 days (page 21). Non-conformity and preventative assessment procedure [redacted] states ERs are raised within 1 business day (page 20) and require justification if not completed within 30 days (page 53). It was unclear during the inspection when each procedure was applicable. It was noted by the inspector that the Management Review applied KPIs for Exception Reporting of 1 day for initiation and 90 days for completion.

2.3.2.2 SOPs appeared to be excessive in length and were confusing to follow, the Exception Records SOP was more than 80 pages, [redacted] was 46 pages.

Reference: EU GMP C1.4(xiv), C1.12, C1.13(ii), C4.3, C4.4

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 deficiencies were outlined in the closing meeting, and the site committed to providing a response within the stated timeframe.

F2 Assessment of response(s) to inspection report

A type 1 post inspection letter (PIL) was issued on 28th September 2023. A response to the PIL was received on 16th October 2023. The response to the PIL was reviewed and a Request for Further Information (RFI01) was issued on 31st October 2023. The response to RFI 01 was received on 13th November 2023 and found generally acceptable.

F3 Documents or Samples taken

None taken.

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

The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
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: 22/12/23**

Accompanying Inspector: [redacted] **Date: 22/12/23**

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

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

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

Risk rating level	Input from current Inspection Findings (last inspection findings applicable to rating 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	

[redacted]

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

[redacted]

[redacted]

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

[redacted]

[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.gov.uk