Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Allergan

MHRA Inspection Number: Insp GPvP 426/118048-0009

10 South Colonnade, Canary Wharf, London E14 4PU **T** 020 3080 6000 **E** gpvpinspectors@mhra.gov.uk
www.gov.uk/mhra

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	For cause National Inspection
System(s) inspected:	Allergan MFL2518
Site(s) of inspection:	Marlow International, Parkway, Marlow SL7 1YL
Main site contact:	[redacted]
Date(s) of inspection:	30 – 31 January 2020
Lead Inspector:	Rory Littlebury
Accompanying Inspector(s):	Dominic Nguyen-Van-Tam Sarah Gomersal
Previous inspection date(s):	24 – 27 Apr 2018 19 – 22 Sep 2016 (on-site) plus 5 inspection days w/c 10 Oct 2016 09 – 11 May 2012 30 Sep – 03 Oct 2003 20 – 23 Aug 2007 15 – 17 Sep 2008
Purpose of inspection:	To verify actions taken with regards to identified missing source documentation for adverse drug reaction reports.
Products selected to provide system examples:	No specific products were selected.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Argus (commercially available)
Key service provider(s):	Archiving provided by Iron Mountain.
Date of final version of report:	23 April 2020
Report author:	Rory Littlebury Senior GPvP Inspector

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SECTION B: BACKGROUND AND SCOPE

B.1 Background information

A for cause inspection of Allergan was conducted as part of the MHRA's statutory, national pharmacovigilance inspection programme, due to concerns which had been raised regarding missing source documentation for specific individual case safety reports (ICSRs) relating to products for which Allergan is and has been an MAH. The purpose of the inspection was to review the actions taken by Allergan to-date to identify possible locations of the source documentation and to agree on the future actions to be undertaken by the company to locate the missing source documents.

A list of reference texts is provided at Appendix I.

Allergan is a global pharmaceutical company, with headquarters in Dublin, Ireland, which focusses on developing, manufacturing and commercialising branded pharmaceuticals, devices and biological products globally. On the 25 June 2019, an announcement was made that the global pharmaceutical organisation Abbvie was to acquire Allergan, however at the time of the inspection, there had been no changes to the Allergan pharmacovigilance system.

The MHRA had identified on two separate inspections of organisations that had acquired products from Allergan (one conducted in 2018 and one in 2019), that there were missing and incomplete source records for specific ICSRs relating to those divested products. This indicated a breach of the legal requirements for record keeping outlined in Commission Implementing Regulation 520/2012 Article 12 and Directive 2001/83/EC (as amended) Article 107, covering all source records since 2012 and Directive 2001/83/EC, Article 104 and Volume 9a 2.2.3.g covering records prior to 2012.

The MHRA GPvP Inspectorate wrote to Allergan on 23 December 2019 requesting information regarding source documentation. A response from Allergan on the 17 January 2020 outlined the actions that had been taken to identify the location of missing records. The MHRA GPvP Inspectorate triggered an inspection based on the information received.

The MHRA GPvP Inspectorate letter and the response from Allergan are included in Appendix II.

B.2 Scope of the inspection

There are legal requirements, as outlined above, for the retention of records relating to pharmacovigilance activities. Source data relating pharmacovigilance activities extending over some period of time to may be requested by competent authorities or be needed by the MAH to support safety evaluation activities and it is essential that the data can be accessed, will be readable and can be easily retrieved.

The scope of the inspection was centred on the missing source documentation for products which had been divested by Allergan. Allergan's due diligence procedures, archiving processes and record retention policies were also within scope.

The inspection was performed at Allergan's offices in Marlow, Buckinghamshire.

The inspection was performed using interviews and document review. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix VI).

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B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 16-Jan-2020) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company during the inspection. An inventory of the documentation provided and reviewed is supplied in Appendix III.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan.

A closing meeting was held to agree on the actions to be taken by Allergan following the inspection, and to confirm the frequency with which updates will be provided to the MHRA. A post-inspection letter was sent to Allergan on the 03 February to confirm the actions which had been agreed during the course of the inspection. This letter is included within Appendix IV of this report, and the actions have been included within section D.1. of this inspection report.

A list of the personnel who attended the closing meeting is contained within documentation which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION OBSERVATIONS

C.1 Summary of significant changes and action taken since the last inspection

This inspection was triggered for the review of a specific concern and therefore did not include a review of routine pharmacovigilance processes. However, the acquisition of Allergan by Abbvie had been announced on the 25 June 2019. As described in Section B.1. there had been no changes to the Allergan pharmacovigilance system at the time of the inspection.

C.2 Reporting of the inspection

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The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

No findings are being reported following this inspection. A finding has been reported against the MAH, Teva, in Inspection report [redacted] Under MA.1. "Pharmacovigilance Data Management". This report serves as a record of the actions taken by Allergan to date, and outlines the agreed approach and actions following the inspection.

This inspection report and its outcomes will be shared with the EMA, other EU competent authorities and the European Commission.

C.3 History of acquisitions related to the inspection scope

This section is a summary of the information provided to the inspection team during the inspection. Further information is detailed within the inspection documentation, filed with the inspection report.

2012 Watson acquired Ascent Pharmahealth, and acquired Actavis Group, adopting the Actavis name.

2013 Actavis acquired Warner Chilcott, retaining the Actavis name.

2014 Actavis acquired Forest Laboratories, including Aptalis

2015 Actavis acquired Allergan Inc, and adopted the name Allergan plc.
Allergan plc acquired Auden McKenzie.

2016 Allergan plc divests the global generics business to Teva in August

C.4 Summary of actions taken by Allergan in relation to source records

Allergan had responded to the MHRAs letter dated 23 December 2019 and outlined a series of actions which had been undertaken to locate the missing source documentation. This covered both products which had been acquired by Allergan and remained within Allergan's pharmacovigilance system, and those that had been divested. The inspection team verified these activities during the inspection.

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Allergan had performed a review of ICSRs in the global safety database for products currently authorised in the UK that had been acquired and were within the Allergan pharmacovigilance system*. The relevant medicinal products investigated were of two [redacted] and [redacted] There were no ICSRs that were missing source documents from the [redacted] products, and three ICSRs out of the total 12,581 that were missing source documents for the linaclotide product. There was no breach of legislation identified, specifically with regards to record-keeping, where Allergan was the MAH.

Allergan also investigated UK authorised products that were acquired since January 2012 and had been subsequently divested. The investigation included searching Allergan's global safety database and Actavis' global safety database to determine the number of ICSRs which did not have source documents attached to them. Over 150,000 ICSRs were identified. A summary is provided for ICSRs associated with each acquired company below:

Forest Laboratories

Allergan identified 10 out of 4,580 ICSRs which did not have source documents associated with them. Allergan were able to locate the source documents for six of the 10 ICSRs, and identified the remaining four as licence partner cases, where the partner would be expected to hold the source document.

Actavis Generics portfolio

Allergan had identified over 97,000 ICSRs from 192,280 which were missing source documents. In January 2020 Allergan requested a line listing from Teva to facilitate locating additional source documents.

Warner Chilcott

In July 2019, Allergan contacted previous employees of Warner Chilcott which stated that any hard copy files would have been transferred from a previous service provider to Warner Chilcott upon close of service. Additionally, in July 2019, Allergan located 100 boxes in an archive in Canada.

In January 2020 Allergan retrieved an archive listing from Archive Solutions, who were used by Proctor & Gamble (prior to the acquisition by Warner Chilcott). This listing contained approximately 450 boxes which could contain source documentation but had not yet been searched.

Allergan had identified 53,907 ICSRs from 66,604 which did not have source documentation.

* Ironwood, a business partner of Allergan, had the responsibility for the global safety database for linaclotide.

C.5 Actions agreed as an outcome of the inspection

Allergan committed to developing a project plan to locate missing source documentation as a result of the inspection and to share this with MHRA GPvP Inspectorate upon its completion. This project plan was received on the 01 April 2020. Allergan's key deliverables have been included below:

- The review of 51 archive boxes retrieved from the Warner Chilcott Canada archive.
- The investigation and review of approximately 450 rows on the archive inventory received from Archive Solutions.
- The review of literature cases which could be recreated from references within cases.
- Teva will provide Allergan with a list of cases where source documents were not initially provided; Allergan will work with Teva to reconcile.
- All actions which have been agreed with Teva following the inspection of Allergan in relation to retrieving missing source documentation:
    - A summary of any changes to the quality management system as a result of the inspection. This should include updates to / new SOPs or guidance documents and changes to current practices.
    - All deviation records which have been raised and the associated CAPA due to changes in the quality management system following the inspection.
- For MHRA request F3, (i.e. it was noted that there were cases where it appeared that there were no source documents attached to the electronic case file in the Argus database). A summary of all investigations taken with regards to why source documentation has not been attached as per current practice will be provided.

The plan has been included in Appendix V.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

Allergan are required to provide updates to the MHRA GPvP Inspection team on a quarterly basis, regarding the status of the project. These quarterly updates should include details of any changes which result from the ongoing activities associated with the acquisition of Allergan by Abbvie.

D.2 Recommendations

The MHRA GPvP Inspectorate will continue to supervise the retrieval of the missing source documents, through the quarterly updates but may also require further onsite, or remote supervision of the activities Allergan have outlined in the project plan.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).

APPENDIX II MHRA AND ALLERGAN CORRESPONDENCE

Initial request for information dated 23 December 2019

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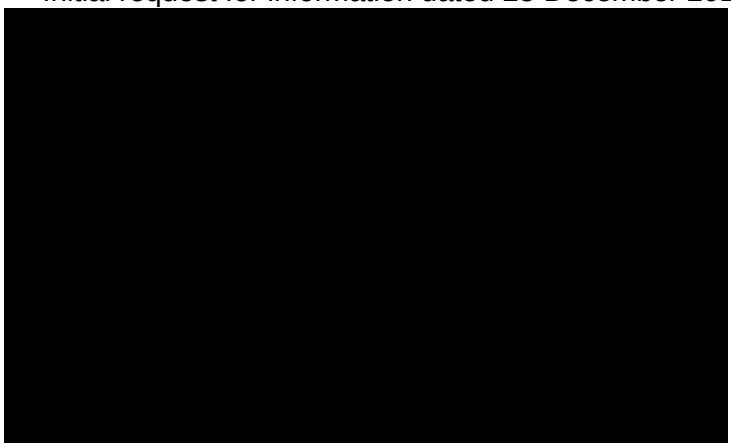

APPENDIX III INVENTORY OF DOCUMENTS REQUESTED AND REVIEWED

[redacted] Section 43

APPENDIX IV POST-INSPECTION LETTER

[redacted]

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APPENDIX V ALLERGAN'S PROPOSED PROJECT PLAN

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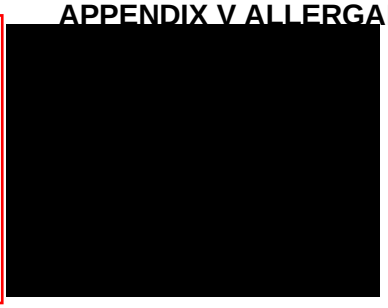

APPENDIX VI PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC		
PHARMACOVIGILANCE INSPECTION OF	Allergan	**DATES**	Thursday 30th January 2020
LOCATION	Allergan Ltd., Marlow International, The Parkway MARLOW Buckinghamshire SL7 1YL, UK	**START TIME**	0900

Inspection plan

This inspection will focus on the issues that have been identified regarding missing adverse event source documentation. To assist in scheduling availability of personnel some interview sessions have been outlined below.

Day 1

09:00 GMT

Opening Meeting

- Review the scope of the inspection.
- Following the opening meeting, Allergan are asked to give a company presentation to provide the inspectors with an overview of the company, including mergers, acquisitions and divestments and a summary of the issues that have emerged regarding missing source documentation for adverse event cases (including when the issue was identified, numbers of cases affected, actions taken etc.). This presentation should last no longer than 40 minutes.

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[redacted]

Document review: Verification of the information provided to the MHRA on 17th January 2020 regarding missing source documents. Please make available all documentation to enable the inspection team to verify the information provided to the MHRA on 17th January 2020. Ad-hoc interview sessions / document explanation may be required (DN).
14:00 GMT **Interview session** at (approximately) to discuss Allergan's proposed actions, timeframes, agreed on-going communication with MHRA regarding missing source documentation and past and current due diligence procedures (RL)
[redacted]
Further document review and ad-hoc interview sessions as required.
Inspection team: Rory Littlebury (RL; Lead Inspector), Dominic Nguyen-Van-Tam (DN), Sarah Gomersal (SG)

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MHRA INSPECTION NUMBER	TBC		
PHARMACOVIGILANCE INSPECTION OF	Allergan	**DATES**	Friday 31st January 2020
LOCATION	Allergan Ltd., Marlow International, The Parkway MARLOW Buckinghamshire SL7 1YL, UK	**START TIME**	0900

Inspection plan

Day 2

Further document review and ad-hoc interview sessions as required.

Closing meeting (all welcome)

Allergan should complete the below with the names and job titles of those staff who will be attending the interview sessions and who will be available during the inspection.

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[redacted]

Other subject matter experts from Allergan sites globally are available for teleconference interview, as necessary.

Inspection team: Rory Littlebury (RL; Lead Inspector), Dominic Nguyen-Van-Tam (DN), Sarah Gomersal (SG)