Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Aurobindo

MHRA Inspection Number: Insp GPvP 19276/293238-0010

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

Table of Contents

ABBREVIATIONS

CAPA	Corrective and Preventative Action
DCP	Decentralised Procedure
EMA	European Medicines Agency
EU	European Union
EUCSI	European Union Core Safety Information
GVP	Good Vigilance Practice
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QPPV	Qualified Person responsible for Pharmacovigilance
SmPC	EU Summary of Product Characteristics
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Section 43

Inspection type:	Statutory National Re-inspection
System(s) inspected:	Milpharm Limited, Aurobindo Pharma Ltd (MFL1655)
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	Remote inspection conducted on 27 – 28 May, 10 June and 18 – 19 June 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	13 – 15 May 2019 23 – 24 August 2011 18 – 20 January 2010 28 – 30 January 2009 17 – 18 November 2008 28 – 30 April 2008 30 October – 01 November 2006
Purpose of inspection:	Re-inspection to determine if appropriate action had been taken from the previous inspection and to review compliance with UK and EU requirements.
Products selected to provide system examples:	The product information, submission of safety variations and PIL into pack implementation was reviewed for a number of nationally authorised products.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Argus Safety Release 8.1.2 (commercially available)
Key service provider(s):	Not applicable – all pharmacovigilance activities are performed by the MAH.
Inspection finding summary:	0 Critical findings 1 Major finding 1 Minor finding
Date of first issue of report to MAH:	24 July 2020
Deadline for submission of responses by MAH:	28 August 2020 23 October 2020
Date(s) of receipt of responses from MAH:	27 August 2020 22 October 2020
Date of final version of report:	29 October 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Aurobindo Pharma Ltd (hereafter 'Aurobindo') was selected for re-inspection as a result of a critical finding that was identified during the previous routine inspection of the MAH, performed on 13 – 15 May 2019. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the previous inspection. In particular, reference was made to Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules. A list of reference texts is provided in Appendix I.

Aurobindo is an international generics company with sales in over 150 countries and holds almost 400 national licences in the UK under the MAHs Milpharm Limited and Aurobindo Pharma Ltd, UK. Since the previous MHRA inspection in May 2019, the MAH had obtained 29 new UK marketing authorisations covering 13 active substances.

Global pharmacovigilance activities are conducted at the Global Pharmacovigilance department in India, including management of ICSRs, global literature searches, monitoring of EudraVigilance data, aggregate report scheduling and production, maintenance of reference safety information including the European Union Core Safety Information (EUCSI), signal management, maintenance of risk management plans, and quality assurance for pharmacovigilance activities. The EU Pharmacovigilance team, based at APL Swift Services Ltd in Malta (part of the Aurobindo group), provides the QPPV and back-up function, maintains the PSMF, and maintains oversight of EU-specific pharmacovigilance activities, including implementation of risk minimisation measures and conduct of pharmacovigilance audits. It also supports the network of Responsible Persons for Pharmacovigilance (RPPs) in EU countries. The RPP for the UK is based at the Aurobindo offices in South Ruislip, Middlesex.

B.2 Scope of the inspection

The inspection focussed on a review of the systems and processes which were associated with the critical finding identified during the previous inspection in relation to the implementation of updates to authorised product information and was performed remotely on 27 – 28 May, 10 June and 18 – 19 June 2020. The inspection was predominantly conducted via document review; however, personnel involved in pharmacovigilance and regulatory affairs activities were available via teleconference throughout the inspection for ad-hoc queries.

The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (v23.0, dated 27 April 2020) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection. The detail of these request is contained within document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. Minor amendments to the Inspection Plan that occurred during the inspection are highlighted using italic text in Appendix II.

A closing meeting was held remotely via teleconference to review the inspection findings on 19 June 2020.

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, 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 FINDINGS

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

Since the previous inspection in May 2019 there had been no significant changes to the pharmacovigilance system.

C.2 Definitions of inspection finding gradings

Critical (CR): a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major (MA): a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor (MI): a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Comment: the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

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.

Findings from any inspection which are graded as critical or major will be shared with the EMA, other EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered directly into the table(s) in section C.4. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

Root Cause Analysis Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
Further Assessment Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
Corrective Action(s) Detail the action(s) taken / proposed to correct the identified deficiency.
Preventative Action(s) Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
Deliverable(s) Detail the specific outputs from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due Date(s) Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Further information relating to inspection responses can be found under 'Inspection outcomes' at: https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp

C.4 Inspection findings

C.4.1 Critical findings

At the time of re-inspection critical deficiencies identified during the previous inspection relating to the process for implementing PILs containing updated safety information into product packs, for updating information available to healthcare professionals and the public via the UK electronic Medicines Compendium website (eMC) and for maintaining the EUCSI in line with the reference product information, had been partially addressed and were no longer considered to be critical findings, although there were still major deficiencies relating to these areas.

C.4.2 Major findings

MA.1 Maintenance and implementation of the product information

Requirements:

Directive 2001/83/EC as amended
Paragraph 40
"*The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.*"

Article 23(3)
"*The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.*"

Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
Chapter II, Article 8 Notification procedure for minor variations of type IA
"*1. […] However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.*"

Article 24 Implementation of variations
"*1. A minor variation of type IA may be implemented any time before completion of the procedures laid down in Articles 8 […].*"

CMDh/CMDv/132/2009 Q&A - List for the submission of variations according to Commission Regulation (EC) 1234/2008 (Revision 56, May 2020)
5.2. What is meant by "implementation" for Type IA variations?
"*[…] For product information, it is when the Company internally approves the revised product information. The revised product information should normally be used in the next packaging run.*"

Volume 2 EudraLex, Pharmaceutical Legislation: Notice to Applicants. Volume 2A - Procedures for marketing authorisation, Chapter 1 Marketing Authorisation (Revision 11, July 2019)
5.1.1 Continuous update of marketing authorisation
"*In this regard, marketing authorisation holders of marketing authorisations granted in accordance with Article 10 or 10c of Directive 2001/83/EC should introduce variations swiftly whenever the marketing authorisation of the reference medicinal product or of the "original" medicinal product is changed to address a safety or efficacy concern.*"

When new information about the benefits and risks of a product become available it is often appropriate to make changes to reference safety information documents, such as such as the summary of product characteristics (SmPC) and patient information leaflet (PIL), so that healthcare professionals and patients are able to use the medicinal product correctly on the basis of full and comprehensive information.

During the inspection, approximately 30 active substances authorised and marketed in the UK were reviewed in relation to the maintenance of the European Union Core Safety

Information (EUCSI), submission of safety variations and/or implementation of the updated product information.

The following findings were noted in relation to control and maintenance of the SmPC and PIL of Aurobindo products:

Section 43

Finding MA.1 a)
The MAH did not submit a safety variation to update the product information of [redacted] with significant safety information that was present in the reference product information. The UK marketing authorisations of [redacted] were authorised in accordance with Article 10(1) and thus subject to the requirements described in EudraLex Notice to Applicants Volume 2A. The product information of the reference products [redacted] dated March 2019) had been updated on 01 February 2019 to add a warning in SmPC section 4.5 regarding the concomitant use of [redacted] with [redacted] inhibitors. During the annual periodic review of the [redacted] EUCSI with the reference product SmPCs, this difference was identified and the EUCSI was updated on 18 September 2019 to include the information. The subsequent comparison between the EUCSI and the UK [redacted] SmPC was conducted on 09 November 2019 and identified meaningful differences between the two documents. However, at the time of the inspection, no safety variation had been submitted yet to update the UK [redacted] SmPC in line with the EUCSI and reference product.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

Section 43

[redacted]
Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.1 b)
There was a delay of eight months in comparing the amlodipine UK SmPC against the updated [redacted] which resulted in the belated submission of a safety variation to update the UK product information.

Section 43

The annual periodic review of the [redacted] EUCSI against the reference product SmPC [redacted] dated 02 February 2018) resulted in an update to the EUCSI (version 2.0.0.0, effective date 10 September 2019); however, a subsequent comparison between the EUCSI and [redacted] UK SmPC [redacted] was not conducted until 20 May 2020. Meaningful differences were identified between the EUCSI and UK SmPC; for example, the EUCSI included a warning about the concomitant use with mTOR inhibitors in SmPC section 4.5 that was missing from the UK SmPC. The safety variation to update the product information with this warning was only submitted during the inspection on 03 June 2020, nine months after the EUCSI was updated.

GPVD-CP-GEN-016 *European Union Core Safety Information (EUCSI)* (version 4.0.0.0., effective 08 April 2019) stated in section 4.6.26 that "*For urgent EUCSI comparisons (e.g. triggered by a safety signal / PRAC) the 10 working day timeline shall be followed and other routine EU CSI comparisons shall be performed within 20 working days*".

Other examples of late EUCSI-UK SmPC comparisons were identified and are summarised in the table below. Even though there was no impact on the timeliness of safety variation submission, these examples illustrate a weakness in the process which could cause delays to variations being submitted:

[redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]	
Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.1 c)

The MAH made the SmPCs and PILs of their UK-authorised products available on the electronic Medicines Compendium (eMC). The following deficiencies were identified in relation to the provision of the current and up-to-date product information on this platform:

i. The MAH had submitted a [redacted] variation on 24 May 2019 to the MHRA to implement the outcome of PSUSA procedure [redacted] to include information regarding the adverse reaction of thrombotic microangiopathy in SmPC section 4.4 and 4.8 and the corresponding PIL sections for [redacted] and [redacted] film-coated tablets [redacted] Following this variation, the SmPC and PIL versions on eMC were not updated within the expected 10 working day deadline:

- At the time of the inspection, the SmPCs (dated 16 October 2017) published on eMC for both strengths were not the current approved product information and were missing the information from the PSUSA outcome that had been included more than 12 months prior.
- The combined PIL that included the information regarding thrombotic microangiopathy was only uploaded to the eMC during the inspection on 03 June 2020 which represented a delay of over 12 months.

ii. There were delays of up to 210 days to update the product information on eMC following implementation of new or updated safety wording via a [redacted] variation were identified:

- The variation to update the product information of [redacted] with PRAC recommended wording regarding sexual dysfunction and drug interactions with [redacted] was submitted to MHRA on 03 July 2019. However, the SmPC and PIL containing this information were only updated on eMC on 11 and 12 February 2020, which constituted a delay of 210 days.

Section 43

- Further examples were seen where the product information published on eMC had not been updated within 10 working days following variation submission as expected by the MHRA:

[redacted]

In the examples cited in the table, the MAH had counted the 10-working day deadline from receipt of the *Notification of Acceptance* of the variation. Aurobindo are reminded that that "*Minor variations of* [redacted] *do not require prior examination by the authorities before they can be implemented by the holder.*" (Official Journal of the European Union, 2013/C 223/01, 2.1.1. Submission of Type IA notifications).

Root Cause Analysis

[redacted]

Section 43

Further Assessment
[redacted]
Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Section 43

Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.1 d)

One batch of [redacted] and one batch of [redacted] were QP-certified but included outdated PILs which had been superseded by an updated version more than six months prior.

Aurobindo submitted a [redacted] variation to the MHRA on 24 May 2019 to implement the outcome of PSUSA procedure [redacted] to include information regarding the adverse reaction of thrombotic microangiopathy in SmPC section 4.4 and 4.8 and the corresponding PIL sections. The cut-off date to certify packs containing the PIL without this safety information was 24 November 2019; however, the two batches of approximately 450 packs each containing the PIL without the information were QP-certified on 17 January 2020, two months after the cut-off date.

The SmPC and PIL of the products were published on eMC but were also not updated at the time of the inspection (refer to finding MA.1 c)).

After consultation with the MHRA Defective Medicines Report Centre and the Patient Information Quality Unit, Aurobindo were informed during the inspection that no further market action regarding these two batches was required.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

C.4.3 Minor findings

MI.1 Preparation and maintenance of the EUCSI

Finding MI.1
There were examples of records documenting the EUCSI and UK SmPC maintenance activities which were missing information or included contradicting information regarding the dates these activities were conducted. As a result, it was unclear when key steps of the process had been completed: i. The template of the EUCSI request form (version 4.0.0.0., effective date 08 April 2019), capturing information on the reference product used, did not include fields to record the dates on which the form was prepared and reviewed. ii. The amlodipine EUCSI/ SmPC comparison form (dated 20 May 2020) required multiple dates to be recorded; however, the following information was missing: • EUCSI issue date was not populated • The box indicating that a variation was required had been selected; however, no date was populated in the field 'variation to be submitted before' • Reviewer name and date had not been entered to confirm actions • Reviewer name and date had not been entered under results. iii. The EUCSI tracker provided during the inspection was dated 14 May 2020 (as stated in the index document to request A12) but it included the outcomes of EUCSI comparisons that occurred after this date.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

Section 43

Section 43

Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
[redacted]	

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.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

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.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP).
- Directives 2001/20/EC and 2005/28/EC in relation to Clinical Trials.
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 19276/293238-0010	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Aurobindo	**DATES**	27 May – *19 June* 2020
N.B. the inspection plan may be subject to change in the lead-up to, or during, the inspection			

This inspection will focus on reviewing the corrective and preventative actions put in place to address the critical finding reported from the 2019 MHRA GPvP inspection and whether these have been effective in resolving the non-compliances.

As a remote inspection, an opening meeting will be held via teleconference. This will be followed by a period of inspector document request and review; deadlines for providing document requests to the inspectors will be specified by the lead inspector but will be no less than 7 days. The lead inspector will provide notification of when the remote inspection is complete and will organise a closing meeting teleconference to provide feedback on any non-compliance identified.

Formal interview sessions with company personnel will not be conducted, however, we request that you provide a designated contact point who can assist with any ad hoc questions from inspectors or arrange calls between inspectors and subject matter experts s as required.

Opening meeting: 27 May 2020

An opening meeting will be held at the start of the inspection by teleconference (TC) on Zoom on the morning of day 1 which will be led by the lead inspector. The agenda will be:

- Review of the scope and arrangements for the inspection
- Aurobindo are asked to lead a company presentation which aims to orientate the inspectors around the implemented CAPA for the critical finding relating to the implementation of updates to the authorised product information. If applicable, please also include a short overview of any significant changes to the pharmacovigilance system since the last MHRA inspection. This presentation should last no longer than 20 minutes.

Inspection topic:

- Implementation of updates to product information: CAPA deliverables from the previous MHRA inspection, including maintenance of the EU Core Safety Information, updates to eMC and PIL into pack implementation
- *TCs took place on 28 May 2020 to discuss ad-hoc queries regarding the maintenance of the product information on the eMC and the EUCSI maintenance process.*

Closing meeting: *19 June 2020*

A closing meeting will be held via teleconference. The date and timing of this meeting will be communicated in due course by the lead inspector.

Aurobindo should complete the below with the names and job titles of the designated contact point and those staff who will be joining the opening meeting.

Section 43

[redacted]