Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Aurobindo

MHRA Inspection Number: Insp GPvP 19276/293238-0009

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Table of Contents

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EU	European Union
EUCSI	European Union Core Safety Information
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
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
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
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:	Statutory National Inspection
System(s) inspected:	Milpharm Limited, Aurobindo Pharma Ltd, [redacted]
Site(s) of inspection:	Aurobindo Pharma ltd, Ares Block, Odyssey Business Park, South Ruislip, Middlesex, HA4 6QD
Main site contact:	[redacted]
Date(s) of inspection:	13 – 15 May 2019
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	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:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the general systems review, risk management systems for [redacted] were examined.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Argus Safety Release 8.1.2
Key service provider(s):	Not applicable – all pharmacovigilance activities are performed by the MAH
Inspection finding summary:	01 Critical finding 02 Major findings
Date of first issue of report to MAH:	07 June 2019
Deadline for submission of responses by MAH:	11 July 2019; 02 September 2019
Date(s) of receipt of responses from MAH:	11 July 2019; 30 August 2019
Date of final version of report:	14 October 2019
Report author:	[redacted]

Section 40 and 43

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Aurobindo Pharma Ltd ('Aurobindo') was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. 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 at Appendix I.

Aurobindo is an international generics company with sales in over 150 countries and holds over 350 national licences in the UK under the MAHs Milpharm Limited and Aurobindo Pharma Ltd, UK.

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 Ruislip site.

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at Aurobindo's offices in Ruislip, Greater London. Personnel from Aurobindo, Milpharm and APL Swift Services attended the Ruislip site in order to participate in the inspection. Personnel from Aurobindo also participated remotely through teleconference.

The inspection was performed using interviews and document review (including outputs from the global safety database and listings of medical information enquiries and product complaints). The systems reviewed during the inspection are highlighted in the inspection plan (attached as Appendix II).

The inspection focused on the risk management system, including routine risk management through the maintenance of authorised product information, i.e. SmPCs and PILs, the implementation of additional risk minimisation measures where required and the quality management system supporting these activities. Topics in relation to data management, including the collection, collation and reporting of ICSRs, signal management and aggregate reporting were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (v18 dated 17 April 2019) 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.

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 to review the inspection findings at Aurobindo UK, Ruislip, on 15 May 2019. 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.

Following the inspection, a post inspection letter was issued to the company on 21 May 2019, to outline the critical finding observed and the immediate actions required. An additional office-based day of inspection was required to complete the review of data requested during the onsite inspection and the information submitted in response to this letter.

SECTION C: INSPECTION FINDINGS

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

Since the previous inspection in 2011 the company had made the following changes to the pharmacovigilance system:

Section 43

- The QPPV changed from [redacted] in June 2013.
- In December 2016, the QPPV and EU Pharmacovigilance team along with the PSMF relocated from the office in Ruislip, UK to Malta.
- The global safety database transitioned from ARISg to Argus on 09 June 2014.
- In November 2018 the employment of the UK RPP was terminated; their replacement was not in post until April 2019. A business continuity Deputy RPP was available during this time covering UK RPP activities and additional support was recruited to support the pharmacovigilance function from February 2019 until April 2019.

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

CR.1 Implementation of updates to authorised 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"*

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 5 Marketing Authorisations, Regulation 76

Commission Implementing Regulation (EU) No 520/2012
Article 11 (1) *"Specific quality system procedures and processes shall be in place in order to ensure the following: […](f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal;"*

Official Journal of the European Union, 2013/C 223/01:
2.1.1. Submission of Type IA notifications *"Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder."*

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 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.

Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions, minimising risks and contributing to the protection of patients' and public health.

Deficiencies were identified in the Aurobindo process for implementing PILs containing updated safety information into product packs and for updating information available to healthcare professionals and the public via the UK electronic Medicines Compendium website (eMC), resulting in delays in providing patients and healthcare professionals with up-to-date information on known product risks. This is considered to adversely affect the rights, safety or well-being of patients and poses a potential risk to public health, consequently, a critical finding has been reported.

Finding	**CR.1 a)**

Aurobindo had failed to ensure that PILs containing updated safety information were being introduced in released batches of product in accordance with the guidance published by the MHRA, which states that, once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months.

https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets

Section 43

In total [redacted] non-compliant batches, involving nine product safety information updates, were identified to have been released containing outdated PILs beyond the maximum six months to implement the updated leaflets. Of these, [redacted] batches were released in excess of nine months after variation approval (or submission for [redacted] variations), which represents a significant delay in implementing the up-to-date PILs.

Specific examples reviewed together with relevant batch records during the inspection are detailed below.

- Examples i), ii), iii) and v) include products for which [redacted] ('do and tell') variations were submitted in relation to safety updates published by the PRAC or by the CMDh, where batches containing significantly out-of-date PILs were released more than nine months after the submission of these variations, well beyond the MHRA expectation that the updated PIL should be implemented within six months of [redacted] variation submission.

- Examples iv) and v) include products for which batches containing significantly out-of-date PILs were released more than nine months after the approval of a [redacted] safety variation to update the PIL with significant safety information.

- The lack of robust processes for control and implementation of up-to-date PILs was further evidenced by the release of batches containing superseded PILs after the batches containing current versions of PILs were released in examples iii), iv) and v).

- In the examples below, the safety updates to the PIL were clinically significant, specifically; the inclusion of potentially fatal adverse reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) (i), toxic epidermal necrolysis (ii), anaphylaxis (iii) and warnings on withdrawal symptoms (v).

i) A variation to update the SmPC and PIL in line with a PRAC recommendation on signals (published 07 August 2017) for [redacted] [redacted] tablets [redacted] was submitted within the PRAC deadline on 04 October 2017. The update to the PIL was to include the side effect of DRESS in section 4.

The last batches [redacted] hat included the superseded PIL [redacted] missing this side effect were released on 10 December 2018, almost 14 months after variation submission.

ii) A variation to update the SmPC and PIL of [redacted] in line with the CMDh position (dated 11 October 2017), following the conclusion of the PRAC assessment of [redacted] was submitted within the CMDh deadline on 24 January 2018. The update to the PIL was to add the side effect of

Section 43

toxic epidermal necrolysis, drug interactions with antibiotics and additional information on the excretion of [redacted] n breast milk.

The last batch [redacted] with the superseded PIL [redacted] was released on 23 November 2018, 10 months after variation submission.

iii) A variation to update the SmPC and PIL for [redacted] in line with the CMDh position (dated 13 December 2017), following the conclusion of the PRAC assessment of [redacted] was submitted within the CMDh deadline on 26 March 2018. The update included the addition of hypersensitivity reactions (angioedema and anaphylaxis) to PIL section 4.

The last batches [redacted] with the superseded PIL [redacted] were released on 21 January 2019, 10 months after the variation submission. It should be noted that the first batch with the updated PIL (P1518175) was released in the meantime on 11 January 2019.

iv) A variation to align existing wording in the SmPC and PIL for [redacted] with the wording of the PRAC assessment report for PSUR procedure [redacted] regarding the risk of angioedema with mTOR inhibitors and drug interactions with [redacted] was approved on 19 March 2018.

The last batches [redacted] containing the superseded PIL [redacted] were released on 08 February 2019, 11 months after variation approval. It should be noted that the first batch with the updated PIL [redacted] was released in the meantime on 03 December 2018.

In total [redacted] packs were released with an out-of-date PIL after the deadline. A deviation [redacted] regarding the release of batches with out-of-date PILs was raised by the service provider APL Swift (responsible for batch release) on 29 November 2018, however the list of batches in the deviation report was incomplete. The impact assessment included a review of the potential risks of releasing the superseded PIL and it was concluded that the medical information is the same and that there was no safety concern. The batches were released; however, no advice or approval was sought from MHRA prior to release of batches. In rare and exceptional circumstances, where an unexpected or unavoidable situation has arisen, the MHRA can consider batch specific variations for the release of products that are not in compliance with the relevant marketing authorisation. More information is available at https://medregs.blog.gov.uk/2017/02/09/when-the-unexpected-happens-batch-specific-variations/

v) Three variations were submitted consecutively to update the SmPC and PIL for [redacted]

- To update in line with the innovator product with the addition of warnings and precautions to the SmPC in relation to addiction and withdrawal symptoms after stopping the product, and in section 4 of the PIL, addition of withdrawal symptoms with an unknown frequency. The Type IB variation [redacted] received RMS approval on 16 November 2017.
- To include a warning regarding dystonia in PIL section 2 'Warnings and Precautions' in line with a PRAC recommendation on signals (published 25 September 2017). The [redacted] variation was submitted within the PRAC deadline on 20 November 2017 [redacted]
- To delete the warning in relation to addiction in line with the Commission

Section 43

Implementing Decision correcting Decision [redacted] The [redacted] variation (dated 15 November 2017) was submitted within the CMDh deadline on 08 January 2018 [redacted]

A change control (change ID [redacted] was opened on 07 February 2018 to cumulatively implement the changes of these three variations into the PIL. Regulatory review of the change control was completed at Aurobindo on 17 March 2018; however, the change control was not closed out until 17 July 2018. The cut-off date for the superseded PIL in the artwork tracking system was incorrectly determined as 07 August 2018, i.e. six months after the approval date of the third variation.

A batch of [redacted] tablets [redacted] containing the superseded PIL [redacted] was released beyond this date on 04 January 2019, 13.5 months after the first variation was approved. It should be noted that the first batch of [redacted] with the updated PIL [redacted] was released in the meantime on 18 October 2018.

Whilst preparing for the inspection, Aurobindo raised a deviation [redacted] dated 08 May 2019) concerning the release of out-of-date PILs in packs from the APL Swift Services batch release site in Malta. A list of affected products and batches was provided by Aurobindo to the MHRA's Defective Medicine Reporting Centre (DMRC); however, this list did not contain all examples that have been identified during this inspection. At the time of inspection, the MAH was still conducting an investigation of the issue and there were [redacted] batches of UK-authorised products (total of [redacted] packs) in quarantine (i.e. not yet released by the QP) at the batch release sites in Malta [redacted] and the UK (Milpharm Limited), and [redacted] batches which were currently in transit from manufacturing sites to batch release sites, which may contain out-of-date PILs. A post inspection letter was sent to Aurobindo on 21 May 2019, to request a full investigation by the company to provide assurance of the compliance of these batches on QP certification. Any non-compliant batches are to be re-packaged or only QP certified and released to the UK market following submission and approval by the MHRA of Type II batch specific variations.

As detailed in the letter, details of the [redacted] released non-compliant batches have been provided to the DMRC by the GPvP inspectorate for consideration of further action which has notified to Aurobindo.

A copy of the post inspection letter and company response, including the investigation conducted by the company, has been appended to this report in Appendix III. The initial response from Aurobindo received on 29 May 2019 regarding the addition of a checklist (in annexure 2) as an additional control after QP certification is unacceptable. In accordance with EudraLex Volume 4, Annex 16 'Certification by a Qualified Person and Batch Release', (date effective 15 April 2016) it is the responsibility of the QP to ensure that the batch is in compliance with the requirements of its MA during certification.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

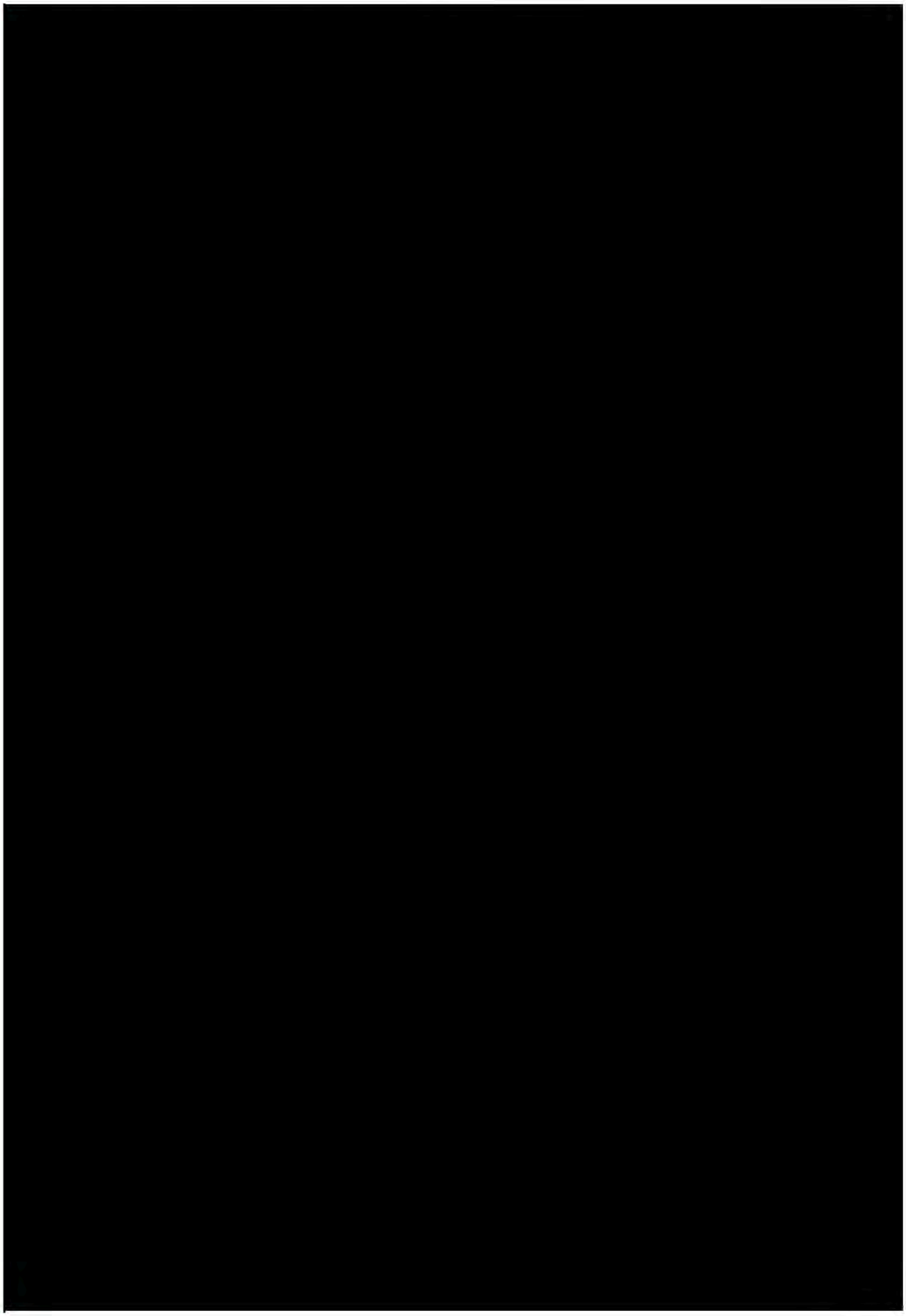
Deliverable(s)	Due Date(s)
[redacted]	

Section 43

Preventative Action(s)

[redacted]

Section 43



Section 43

[redacted]

Section 43

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

Finding CR.1 b)

Aurobindo published information on its marketed products through the UK eMC website, however examples were identified where Aurobindo had failed to keep this information up-to-date.

i) In relation to the examples presented in finding CR.1a) above, describing safety updates for which out-of-date PILs had been released, there were significant delays of up to one year in updating the authorised product information available to healthcare professionals and patients published on the eMC.

Section 43

Example	Date of approval (Type IB)/submission (Type IA/IA_{IN})	Date of submission for upload to eMC	Delay (approx.)
[redacted]			

ii) The SmPC and PIL for [redacted] tablets [redacted] on eMC was not the current approved product information. Variation [redacted] was approved on 10 October 2017 and included an update to SPC section 4.4 *Special warnings and precautions for use* and 4.5 *Interaction with other medicinal products and other forms of interaction* regarding dysglycaemia and poor blood glucose control during concomitant use with fluoroquinolones and St John's Wort respectively.

This finding is also compounded by the release of a batch of [redacted] which contained the superseded version of the PIL on 22 April 2018, more than 6 months after the variation was approved (12 days beyond the deadline to implement the new version). It was noted that eMC was updated with the 2017 versions following the inspection, on 15 May 2019.

iii) Further examples were seen where the product information published on eMC had not been updated within 10 working days following regulatory approval of a safety update:

- There was a delay of 3.5 months to update the SmPC and PIL for [redacted] mg film-coated tablets on eMC (update request submitted to eMC on 01 June 2018) following approval of procedure [redacted] on 21 February 2018. The procedure included the addition of a drug interaction with [redacted] and to align the wording in SPC section 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, and 5.2 with the product information of the reference product.

- There was a delay of 3 months to update the SmPC and PIL for [redacted] Film-coated tablets on eMC (update request submitted to eMC on 01 June 2018) following approval of procedure [redacted] on 09 March 2018. The procedure included the addition of a warning regarding the risk of angioedema with concomitant use of mTOR inhibitors and the addition of the drug interaction with [redacted]

- There was a delay of 3 months to update the SmPC and PIL [redacted] capsules on eMC (update request submitted to eMC on 29 October 2018)

Section 43

following approval of procedure [redacted] on 19 July 2018 and of procedure [redacted] on 27 July 2018.

Procedure [redacted] ncluded the addition of warnings regarding the withdrawal of [redacted] the risk of opioid toxicity in patients with deficient CYP2D6 metabolism, the use in children post-operatively and in children with compromised respiratory function. Procedure [redacted] ncluded the addition of a warning and drug interaction regarding the risk of respiratory depression and sedation with the concomitant use of sedative medicines, such as [redacted]

SOP [redacted] 'Electronic Medicines Compendium (eMC) Maintenance' (revision 02, date effective 08 June 2018 and revision 01, date effective 03 January 2018) stated in section 4 Responsibilities: *"Commercialised products already granted in UK portfolio: within 10 working days after receipt of an approval from UK authority or European medicines authority approving the change"*, which is in line with MHRA expectations.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

Preventative Action(s)
[redacted]

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

The following deficiency was identified in the company's written procedures relating to the maintenance of reference safety information, which had potential to introduce delays into the maintenance of reference safety information for products.

Finding CR.1 c)

Aurobindo had created European Union Core Safety Information (EUCSI) for each of its products authorised in the EU. However, there was no procedural requirement to carry out comparisons of the EUCSI against the reference medicinal products until the requirement for annual review was incorporated into an updated version of GPVD-CP-GEN-016, 'European Union Core Safety Information (EUSCI)' v4.0.0.0 (Section 4.17 Annual Periodic Review) effective 08 April 2019.

This led to delays in comparisons with the reference product taking place and therefore delays in updating the EUCSI and national product information accordingly, where required.

According to the change history, the Risedronate EUCSI v1.0 (effective 12 September 2016) was updated in April 2019 (effective 30 April 2019) as a result of comparison with the reference product. The innovator product SmPC used for the comparison had a date of revision of the text of 14 January 2016.

The following table shows examples of EUCSI approved in 2016 but where review of the authorised product information for the reference product was not planned until May 2019.

INNs	Current EUCSI status	Current version	Effective Date	Annual Periodic Safety Review-Planned Date
[redacted]				

Section 43

[redacted]

It is noted that at the time of the inspection, a schedule for review of the EUCSI for all products had been put in place and that EUCSI review against innovator products for all UK approved products was scheduled for completion by April 2020.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Section 43

[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)

Section 43

[redacted]

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

C.4.2 Major findings

MA.1 Risk management

Requirements:

Directive 2001/83/EC as amended, Article 104(2) and
(3) *"As part of the pharmacovigilance system, the marketing authorisation holder shall:* [...] *(d) monitor the outcome of risk minimisation measures which are contained in the risk management plan"*

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulations 182(2) *"The holder must (as part of its pharmacovigilance system) [...] (c) operate a risk management system for the product in accordance with the risk management plan (if any) for the product"*

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)
XVI.B.4. *"Evaluating the effectiveness of additional risk minimisation measures is necessary to establish whether an intervention has been effective or not, and if not why not and which corrective actions are necessary."*
XVI.B.6. *"These records, the RMP and the associated risk management systems, as well as any documents on risk minimisation measures may be subject to audit or inspection."*

A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions. Risk management is applicable to medicinal products at any point in their lifecycle. The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. The majority of safety concerns are addressed by routine risk minimisation measures. Exceptionally, for selected important risks, routine risk minimisation may be considered insufficient and additional risk minimisation measures (aRMMs) may be deemed necessary.

The following finding were noted in relation to risk management systems:

Section 43

Finding MA.1

Aurobindo had failed to monitor the effectiveness of the additional risk minimisation measures in the UK for [redacted]

The RMP for [redacted] (v3.0, dated 02 August 2016), outlined the controlled distribution system for the product, to ensure all prescribers are informed about the appropriate use of bosentan. In the UK, according to the controlled distribution plan agreed with the MHRA, covering UK Mainland (CESW) (v2.0, dated January 2019), when a hospital expresses interest through the Milpharm sales team to obtain [redacted] or any indication, the relevant email is forwarded to the UK RPP. The educational materials are sent to the interested party together with a standard email to inform them about the controlled distribution. On receipt of confirmation of the materials, the hospital is added to the approved prescribers

Section 43

list, which is provided to the distributo[redacted] The plan additionally stated:

"Every 3-months from start of the first shipping, [redacted] will provide full list of orders for reconciliation with Milpharm Sales department. Milpharm Sales would perform a control of the listed prescribers and the shipped orders, to ensure that the distribution has been controlled, and is restricted to an approved list of prescribers."

There was insufficient evidence to support that this reconciliation with [redacted] which is a mechanism for monitoring the effectiveness of the controlled distribution, was conducted in accordance with the approved controlled distribution plan.

- In response to a request for evidence of this activity (document request U4), emails were provided dated 22 March 2018 and 27 July 2018 showing requests made for data from [redacted] in order to conduct this reconciliation for Q1 and Q2 2018 respectively, however there was no documented outcome of this activity.

- Additionally, in response to document request U4, documents purporting to demonstrate the reconciliation for Q4 2018 and Q1 2019, which contained signatures dated 04 January 2019 and 05 April 2019 for their preparation, and 07 January 2019 and 05 April 2019 for their review, respectively, were provided. Subsequently a statement prepared and signed by personnel from Aurobindo including the EU QPPV and the UK Managing Director during the inspection on 15 May 2019 confirmed that these documents had not been signed contemporaneously but had been signed during the inspection on 15 May 2019. The statement concluded:

  "The provided reconciliation reports, which have been created on 15/5/2019 as evidence on previous conduced reconciliation and dated as per internal meetings is misleading, as without document note the dates on the document represent the actual meetings lead to the conclusion that the documents had been signed on the dates recorded, which is not the case."

- Aside from handwritten notes stating [redacted] and [redacted] shown to inspectors on the relevant dates in a diary and in a note book of relevant personnel, there was no other documentation to confirm that the reconciliation activities had occurred in Q4 2018 or Q1 2019.

The MAH is reminded that under The Human Medicines Regulations, Regulation 208, it is an offence to provide *"information to the licensing authority or the EMA, pursuant to an obligation in the Part* [Part 11 Pharmacovigilance], *but that information is false or misleading in a material particular"*. Care should be taken when signing and dating documents so as not to misrepresent documents as contemporaneous when they have been created after the fact.

From a review of shipments in 2018, inspectors identified one instance of a shipment of bosentan that was outside of the controlled distribution mechanism. Order [redacted] was shipped to Queen Elizabeth Hospital Birmingham on 17 August 2018, prior to receipt on 22 Aug 2018 of confirmation that the educational materials had been read and understood. Educational materials had been sent to the University Hospitals Birmingham NHS Foundation trust (which covers Queen Elizabeth Hospital Birmingham) on 21 June 2018.

Section 43

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

Section 43

[redacted]

Section 43

[redacted]

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

Preventative Action(s)

[redacted]

Section 43

[redacted]

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

MA.2 Pharmacovigilance system master file

Requirements:

Commission Implementing Regulation No. 520/2012 Article 4(3) *"Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved."*

Section 43

Finding MA.2

Aurobindo operated two quality management systems, one at a global level and one at an EU level. Examples of relevant pharmacovigilance deviations managed in the global quality management system were identified that had not been presented in the PSMF:

- [redacted] was an open deviation initially recorded in the quality management system on 01 December 2018, relating to *"Preparation of Signal Management Reports were missed for two molecules* [redacted] *and* [redacted] *rom April DLP 2018 list"*. The [redacted] combination product is authorised in the EU.
- [redacted] was an open deviation initiated on 01 February 2019, concerning *"25 case numbers did not auto-generate in Argus Safety 8.1.2 in December 2018"*. The validated Argus database automatically created case numbers sequentially for cases as they were initiated in the database, however during a reconciliation activity it was identified that there were gaps in the sequence without explanation. A service request was raised with Oracle support on 06 March 2019 and was pending a response. The impact of the misfunctioning of this validated system was not known at the time of the inspection.

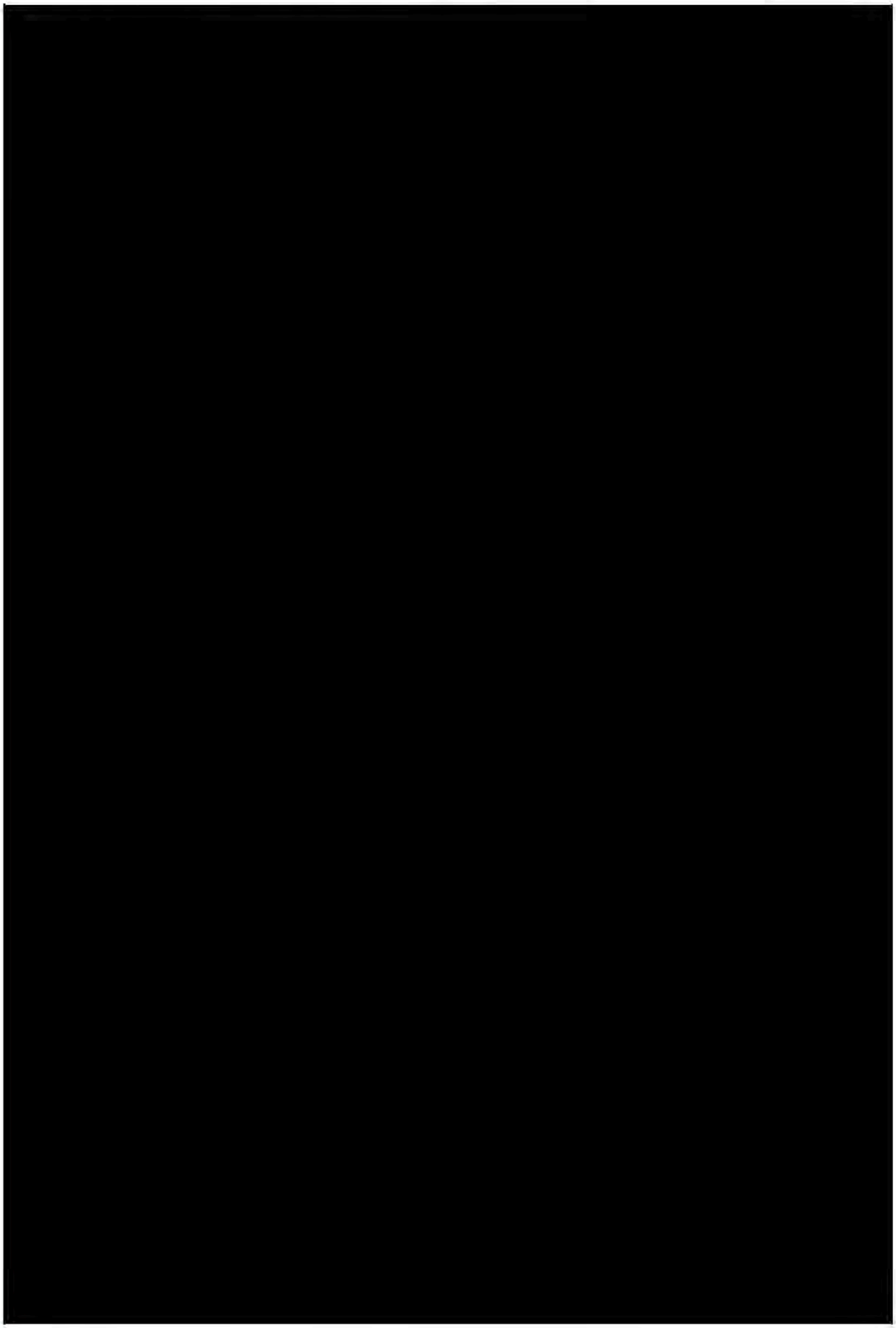
Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43



Section 43

[redacted]

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

Given the nature of the critical inspection finding, the Lead Inspector has recommended that the next MHRA pharmacovigilance inspection is performed within the next 12 months, to review the impact of the actions taken in response to the inspection findings.

APPENDIX I REFERENCE TEXTS

- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- Official Journal of the European Union, 2013/C 223/01, Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures
- CMDh Q&A - List for the submission of variations according to Commission Regulation (EC) 1234/2008

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 19276/293238-0009	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Milpharm/Aurobindo	**DATE**	13 May 2019
LOCATION	Ares Block, Odyssey Business Park, South Ruislip, Middlesex, HA4 6QD	**START TIME**	9.00 arrival for 9.30 start

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system, the quality system and areas undergoing remedial activities *(approx. 20 minutes)*	[redacted]	[redacted]
Collation of documents and document review	-	
LUNCH	-	

Section 40

Section 40

Implementation of additional risk minimisation measures Including but not limited to: - Oversight and compliance management of risk management plan commitments - Specific activities in relation to voriconazole and bosentan	[redacted]	[redacted]
Document review	-	Inspectors only

[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 19276/293238-0009	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Milpharm/Aurobindo	**DATE**	14 May 2019
LOCATION	Ares Block, Odyssey Business Park, South Ruislip, Middlesex, HA4 6QD	**START TIME**	9.00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review	-	Inspectors only
Maintenance of reference safety information - Identification of required updates from various sources - Submission of safety variations	[redacted]	[redacted]
LUNCH	-	-

Section 40

Section 40

Safety communication - Implementation of approved updates to product information – including patient information leaflets and online sources of information - Direct healthcare professional communications	[redacted]	[redacted]
Supervision and oversight of the pharmacovigilance system by the MAH and by the QPPV *Including management and identification of non-compliance through audits and key performance indicators*		[redacted]
Document review	-	Inspectors only

MHRA INSPECTION NUMBER	Insp GPvP 19276/293238-0009	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Milpharm/Aurobindo	**DATE**	15 May 2019
LOCATION	Ares Block, Odyssey Business Park, South Ruislip, Middlesex, HA4 6QD	**START TIME**	9.00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
~~**Supervision and oversight of the pharmacovigilance system by the MAH and by the QPPV**~~ ~~Including management and identification of non-compliance through audits and key performance indicators~~	[redacted]	[redacted]
Document review and ad hoc interview sessions as required	-	
LUNCH	-	-
Document review and ad hoc interview sessions as required	-	Inspectors only
Inspectors meeting	-	Inspectors only
Closing meeting	-	All welcome

Section 40

APPENDIX III POST INSPECTION INVESTIGATION

Section 43

[redacted]