Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Cipla (EU) Ltd

MHRA Inspection Number: Insp GPvP 36390/1480807-0002

151 Buckingham Palace Road London SW1W 9SZ UK
T 020 3080 6000 **E** gpvpinspectors@mhra.gsi.gov.uk www.gov.uk/mhra

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
EMA	European Medicines Agency
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
PASS	Post-authorisation Safety Study
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Updates Reports
QA	Quality Assurance
QPPV	Qualified Person responsible for Pharmacovigilance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Re-inspection
Name and address(es) of site(s) inspected:	Cipla (EU) Ltd C/O APCER Pharma (Europe) Ltd, 9th Floor, CP House, 97-107 Uxbridge Road, Ealing, W5 5TL. NB: The inspection was performed at the offices of the pharmacovigilance service provider.
Main site contact:	[redacted] Address as above [redacted] [redacted]
Date(s) of inspection:	08 - 10 December 2015
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	24 – 26 June 2014
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:	This inspection was a general systems review and ADR reports were examined for a range of products.
Name and location of EU/EEA qualified person for pharmacovigilance:	[redacted] Contact details as above
Global PV database (in use at the time of the inspection):	ARISg (commercially available) version 5.1.2.3 ARGUS (commercially available)
Key service provider(s):	Pharmacovigilance services for safety information originating within the EU provided by APCER Pharma (Europe) Limited (EU-QPPV, global safety database maintenance, PSUR writing, signal detection).
Inspection finding summary:	2 Critical findings 4 Major findings
Date of first issue of report to MAH	05 February 2016
Deadline for submission of responses by MAH	Initial responses: 11 March 2016 Second responses: 10 May 2016 (extension granted) Third responses: 26 May 2016
Date(s) of receipt of	Initial responses: 09 March 2016

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responses from MAH	Second responses: 10 May 2016 Third responses: 25 May 2016
Date of final version of report	11 June 2016
Report author	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Cipla (EU) Ltd was selected for re-inspection as a result of one critical finding that was identified during the previous routine inspection of the Marketing Authorisation Holder (MAH), performed on 24, 25 and 26 June 2014. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the previous inspection. In addition, the inspection provided an opportunity to re-examine the overall compliance of the pharmacovigilance system 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.

Cipla (EU) Limited is a subsidiary of the parent company Cipla Limited, a company headquartered in Mumbai, India, which is also the location of global pharmacovigilance activities. Within the EU, marketing authorisations are also held by other Cipla subsidiaries, Cipla (UK) Limited, Cipla NV and Cipla Croatia. Cipla Limited is focused on the manufacture and distribution of generic medicines Cipla Limited also hold authorisations outside of the EU in territories such as the US, Asia Pacific and Africa.

Pharmacovigilance activities for Cipla (EU) Ltd and Cipla NV, including QPPV services, are outsourced to APCER Pharma (EU) Limited. Much of the activity was conducted at APCER's New Delhi office; for instance, case processing (including data entry, quality control and medical review), compilation of aggregate reports (including PSURs), literature monitoring, compilation and maintenance of risk management plans, training and responding to medical information enquiries and identifying associated adverse events. Submission of expedited reports and PSURs was undertaken by APCER's UK office, in addition to compliance monitoring and maintenance of the PSUR schedule and PSMF. With the exception of literature monitoring, all of these activities were limited to safety information originating within the EEA.

Pharmacovigilance activities for Cipla (UK) Ltd, including QPPV services, are outsourced to S&D Pharma CZ. Cipla (UK) Ltd primarily markets product in central and Eastern Europe. This system was described in overview, and inspected in the context of exchange of safety case data exchange for common active products (with the Cipla/APCER PV system). During the inspection, it was clear that Cipla UK products are supervised via this separate PV system, which should be examined further via a separate inspection.

Pharmacovigilance activities concerning safety information originating outside the EU were undertaken by Cipla Drug Safety Division (DSD) based in India. This included case processing (including data entry, quality control and medical review), compilation of aggregate reports (including PSURs) and literature monitoring.

B.2 Scope of the inspection

The inspection focussed on a review of the systems and processes which were associated with the deficiencies/critical and major findings identified during the previous inspection.
The inspection was performed at the offices of the pharmacovigilance service provider APCER Pharma (Europe) Ltd, in Ealing, Greater London. Personnel from Cipla and APCER attended the Ealing site in order to participate in the inspection. The services of S&D for Cipla UK products were not examined in detail.

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 Pharmacovigilance Inspection Plan (attached as Appendix II).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF to assist with inspection planning and preparation. SDEAs, SOPs, line listings of all worldwide case reports and a project plan for data transferred from Cipla (EU) Ltd and Cipla NV pharmacovigilance databases (managed by APCER) and Cipla (UK) Ltd pharmacovigilance databases (managed by S&D Pharma) to the Cipla Ltd DSD pharmacovigilance database (ARGUS based system) 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 (attached as Appendix II). The quality management system (QMS) session was not explored in sufficient detail and this should be explored further at the next inspection.

Details of adverse reaction reports reviewed during the inspection for specific products are contained in the inspection notes.

A closing meeting was held to review the inspection findings, at the offices of APCER (Europe) Ltd, Ealing on 10 December 2016. 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 the company had made the following changes to the pharmacovigilance system:

- Migration of data from the Cipla (UK) Ltd safety database (managed by S&D Pharma) to the Cipla Ltd DSD safety database managed in India.
- Migration of data from the CIPLA Croatia safety database to the Cipla (EU) Ltd safety database managed by APCER Pharma.
- Implementation of a multipartite SDEA between Cipla Ltd, APCER Pharma and S&D Pharma.

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 at: https://www.gov.uk/good-pharmacovigilance-practice-gpvp#actions-after-the-inspection

C.4 Inspection findings

C.4.1 Critical findings

The critical finding identified during the previous inspection relating to the failure to establish a global pharmacovigilance had not been sufficiently addressed and therefore it remained as a critical deficiency.

CR.1 Failure to establish a global pharmacovigilance system

Requirements:

Directive 2001/83/EC as amended, 107(1);

"Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study. Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union."

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, s187 (4);

"The holder must ensure that reports recorded under paragraph (1) are accessible (electronically or physically) at a single point within the EEA."

Commission Implementing Regulation (EU) No. 520/2012, Article 12 (1);

"Marketing authorisation holders shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information".

GVP Module I – Pharmacovigilance systems and their quality systems, I.B.10.

"The record management system should support:

- the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- timely access to all records;
- effective internal and external communication; and
- the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods"

GVP Module VI – Management and reporting of adverse reactions to medicinal products, VI.C.2.2;

"Each marketing authorisation holder shall have in place a system for the collection and recording of all reports of suspected adverse reactions which are brought to its attention, whether reported spontaneously by healthcare professionals or consumers or occurring in the context of a post-authorisation study. All those reports shall be accessible at a single

point within the Union".

GVP Module VII – Periodic Safety Update Report.

The finding of failure to establish a global pharmacovigilance system recorded at the last pharmacovigilance inspection was not resolved.

There were multiple pharmacovigilance systems in place to support the Cipla product portfolio;

- One system incorporated all products authorised to Cipla (EU) Limited and Cipla Europe NV. This system was maintained by APCER on behalf of the MAH and was hosted in the UK. This system collected and reviewed data originating in the EU. Adverse event data was collected and entered into an ARISg database.
- A second system was maintained by the Cipla headquarter organisation, based in India, which collected and reviewed data originating from Cipla (UK) Ltd products (mostly marketed in central and eastern Europe) all non-EU territories. AE data was collected and entered into an ARGUS database.

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- A third system where pharmacovigilance data in relation to Cipla oncology products was held by the service provider Kohne Pharma GmbH. The service agreement between Cipla and Kohne Pharma was terminated on 30 August 2013.

The above systems had pharmacovigilance data relating to product licences with common active substances help by different Cipla subsidiaries. Thus, the MAH had failed to establish a global pharmacovigilance system. This affected the MAH's ability to access all pharmacovigilance data for the purposes of PSUR production and signal detection. Deficiencies are outlined below.

Finding CR.1 a)

As part of the CAPA from the previous inspection (finding C.4.1 a), the MAH committed to implementing an integrated safety database which held pharmacovigilance data from all Cipla subsidiaries as listed in the finding preamble. At the time of the inspection, this activity had not been completed.

i. Cipla (EU) Ltd, Cipla Europe NV and Cipla Croatia data was held on the ARISg database which was managed by APCER. This was due to be migrated to the Cipla Ltd ARGUS database by 30 June 2015 according to the CAPA from the previous inspection finding (CR. 1. a)). This migration had not happened at the time of the inspection. A statement of work between Cipla Ltd and [redacted] (a company specialising in medical informatics), detailing the migration of data between databases, was not signed until 30 November 2015. It was stated during the inspection that the transfer of data was not expected to be completed until March 2016.

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ii. Data from Cipla (UK) Ltd., which was held on the database of the pharmacovigilance service provider S&D Pharma, was scheduled to be migrated to the Cipla Ltd ARGUS by 30 June 2015 as per the CAPA in the previous inspection report. This data was not migrated until November 2015. This data was not migrated in a complete and accurate manner (see finding CR.1 b)).

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

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Finding CR.1 b)

The following deficiencies were observed with the pharmacovigilance data migrated from the Cipla (UK) Ltd database to the Cipla Ltd ARGUS database;

i. No process documentation detailing the migration of data between the databases existed.

ii. There were examples where data which was migrated to the ARGUS database did not reflect source documentation, namely;

a) [redacted] - Source data provided to the inspection team describes intravenous (IV) formulation for suspect drug [redacted] the CIOMS generated from ARGUS describes tablet formulation. The route of administration was described as IV.

b) [redacted] – Source data provided to the inspection team described liver function test (LFT) results, the CIOMS generated from ARGUS does not contain LFT results and the narrative states that details about diagnostic testing were not reported.

c) [redacted] – Source data provided to the inspection team did not state that all events have resolved, the CIOMS form from ARGUS contained a statement that all events had resolved on an unknown date.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

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Preventative Action(s)

[redacted]

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

Finding CR.1 c)

Pharmacovigilance data relating to Cipla oncology portfolio was held by a service provider known as Kohne Pharma GmbH. The last service agreement between Cipla Ltd and Kohne Pharma was terminated on 30 August 2013. Cipla Ltd and the EU QPPV did not have access to this data. Hence this data could not be readily accessed for the purposes of signal detection of PSUR production. The following numbers of cases for products with common active ingredients also held by other Cipla subsidiaries were found to have resided with Kohne Pharma GmbH;

Product	Number of cases
[redacted]	[redacted]
[redacted]	[redacted]

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

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[redacted]

Preventative Action(s)
[redacted]

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

Finding CR.1 d)
Cipla acquired Croatian based pharmaceutical distributor, Celeris d.O.O in 2013. The company was subsequently renamed as Cipla Croatia d.O.O. However data from the legacy Cipla Croatia pharmacovigilance database was not transferred to the Cipla (EU) Ltd pharmacovigilance database managed by APCER (ARISg) until 16 November 2015. It should be noted that even though this data was transferred to the Cipla (EU) Ltd pharmacovigilance database, it still resided outside of the Cipla Ltd DSD ARGUS safety database (see finding CR.1 a)).

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Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

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[redacted]

Preventative Action(s)

[redacted]

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

Finding CR.1 e)

As deficiencies in data migration and data residing outside of the pharmacovigilance system, PSUR preparation and signal detection activities could not be conducted on a global dataset.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

Preventative Action(s)

[redacted]

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

CR.2 Pharmacovigilance System Description and Documentation – Supervision and oversight

Requirements:

Rights of an Inspector

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 16 Enforcement, s327 (1), (2) and (4) and s334 (3);

"s327 (1) An inspector may inspect anything mentioned in paragraph (2)

(a) in order to determine whether there has been a contravention of any provision of these Regulations…

(2) The things mentioned in paragraph (1) are—

(i) information and documents relating to the safety of medicinal products, including information and documents relating to compliance with—

(ii) the requirements of Part 11 (pharmacovigilance)

(4) The inspector may for the purposes specified in paragraph (1) require a person carrying on a business which consists of or includes the manufacture, assembly, importation, sale, supply or advertising of, or wholesale dealing in, medicinal products, or a person employed in connection with such a business, to produce information or documents relating to the business which are in the person's possession or under the person's control

s334 (3) It is an offence for a person—

(a) intentionally to obstruct an inspector;

(b) intentionally to fail to comply with a requirement properly made under regulation 327 by an inspector; or

(c) without reasonable cause, to fail to give an inspector any other assistance or information which the inspector may reasonably require in order to perform a function under these Regulations."

Pharmacovigilance System Master File

Directive 2001/83/EC as amended, Article 104 (3(b)).

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 182.

Commission Implementing Regulation (EU) No. 520/2012, Chapter I.

GVP Module II – Pharmacovigilance system master file.

"II.B.1. The pharmacovigilance system master file shall describe the pharmacovigilance system and support/document its compliance with the requirements. As well as fulfilling the requirements for a pharmacovigilance system master file laid down in the legislation and guidance, it shall also contribute to the appropriate planning and conduct of […] inspections or other verification of compliance by national competent authorities.

II.B.4.3. The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorised in the EU. This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the pharmacovigilance system master file. Information about third parties (licence partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements.

For the purposes of inspection […] of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorisation holder through which ICSRs could be reported.

The list should describe, on a worldwide basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organised per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years

II.C.2. The pharmacovigilance system master file shall be maintained in a current state and be permanently available to the QPPV […] It shall also be permanently available for inspection."

The failures in provision of documentation to describe the PV system were a significant impediment to the inspection process, in both the planning and preparation (risk assessment and logistics) and the conduct. The extent of the gaps in the PSMF, the inaccuracy and delays encountered were indicative of a lack of oversight and control over the system. A serious breach of legislation is reported, with impact on supervision by the MHRA, and oversight by the QPPV.

Finding CR.2 a)

The PSMF [redacted] provided to the inspection team prior to the inspection was not accurate or complete description of the pharmacovigilance system. Not all sources of safety information were included in the PSMF. The following deficiencies were identified;

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i. Not all service providers were listed in Annex B of the PSMF (Organisational structure and list of business partners), namely;

- PAREXEL International who were responsible for medical monitoring of the ongoing clinical trial in relation to evaluate the bioequivalence of [redacted] manufactured by Cipla Ltd, India (test product) with [redacted] supplied by [redacted] (reference product).
- Synowledge who are responsible for providing call centre services in the USA and receipt of adverse events from the public and prescribers.
- Kohne Pharma GmbH who was responsible for providing pharmacovigilance services for Cipla Ltd oncology products. The agreement with Kohne was terminated on 30 August 2013, however pharmacovigilance data was still held by Kohne at the time of inspection.
- RegSana, who were responsible for providing call centre services for the receipt of medicines information queries in Hungary.

ii. At least 152 business partners fulfilling tasks outside of the EU were listed in Annex B of the PSMF (Organisational structure and list of business partners). The roles undertaken by these partners and the concerned products were not listed.

iii. Not all Cipla affiliate offices who marketed products authorised in the EU were included in Annex C of the PSMF (Sources of safety data), those identified as not being listed are indicated below;

- Cipla USA Inc.
- Cipla Medpro South Africa (Pty) Ltd
- Cipla Australia (Pty) Ltd
- Cipla Malaysia Sdn. Bhd
- Cipla Myanmar
- Cipla Quality Chemical Industries Ltd.-Uganda
- Breathfree-Cipla Subsidiary in Srilanka
- Cipla Vietnam
- Cipla UAE
- Cipla Limited Sucursal Colombia
- A list of Cipla offices globally was requested on the morning of 08 December 2015 (request E1), however, this was not provided until the morning of 10 December 2015.

iv. The list of sources of safety data included in Annex C of the PSMF (Sources of

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safety data) did not contain studies listed below;

- A completed bioequivalence study of [redacted] (Cipla Ltd, India) and [redacted]
- An ongoing bioequivalence study (at the time of inspection) to compare the bronchoprotective Effects of the test Product [redacted] (Cipla, Ltd, India) with the Reference Product, [redacted]
- A completed bioequivalence study to evaluate the efficacy and safety of single dose of 4.5 mcg and 9 mcg of tiotropium dry powder delivered via the [redacted] device (Cipla Ltd.) in comparison with [redacted]

The response to the inspection findings should include information about the LPLV for each of the completed studies and the date of the Clinical study reports for completed studies, as well as an assessment of the completeness and correctness of reporting of ICSRs from these sources.

A complete list of worldwide clinical trials ongoing or completed within the last two years for products with active substances contained in Cipla products authorised in the EU was requested on the morning of 08 December 2015 (request E6), however, this was not provided until the morning of 10 December 2015.

v. The main body of the PSMF relating to computerised systems did not list the Cipla Ltd global safety database (ARGUS).

vi. The separate PSMF for Cipla UK was not properly cross referenced.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

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

Finding CR.2 b)
Documentation provided in pre-inspection document requests and requested during the inspection was incomplete or provided with delay. For example; i. As per request A5 (requested as part of the pre-inspection document requests), the line listing of all worldwide case reports for Cipla products with authorisation in the UK was requested. The listing provided was incomplete and did not contain pregnancy cases or cases which resulted in death. Despite a re-request for a complete dataset on day one of the inspection, the MAH did not provide a complete and accurate dataset. Further errors in the dataset provided included over 200 rows

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being used to represent one case and cases where the country of reporter was listed with a null value (corrected in a subsequent document request). This meant that the data provided was virtually unusable by the inspection team.

ii. The handling of cases had resulted in implausibly high numbers of 'non-valid' cases due to a lack of patient identifiers, which the MAH have been unable to provide a satisfactory explanation for.

Of the 1,996 adverse events on the Cipla Ltd DSD pharmacovigilance database at the time of inspection, around half of them are deemed to be non-reportable due to lack of patient identifiers. The MAH provided an explanation for such a high number of cases with no patient identifiers on the 22 December 2015, which stated that the majority of cases were from literature articles which did not have individual patient identifiers. The MAH needs to explain further whether the articles have been obtained and reviewed in full and if case follow-up is being attempted. The definition of an identifiable patient is too narrowly defined in Cipla Ltd SOP [redacted] as it did not include instances where a patient could be identified via clinical data or a prescriber indicating that the case relates to a patient under his/her care.

Due to the limited time for review on inspection, it remains unclear if the MAH are creating cases correctly and conducting effective follow-up

iii. As per request [redacted] (requested as part of the pre-inspection document requests), volume of sales data on a worldwide basis for all Cipla products with an active ingredient authorised by one of the Cipla group of countries in the UK was requested. Sales data outside of the European Union was not provided.

iv. As per request [redacted] (requested on 08 December 2015), the Synowledge SOP [redacted] was requested. The documentation provided did not include Annexure 2, non-valid call log.

v. As per request [redacted] (requested as part of the pre-inspection document requests), a list of approved variations affecting PILs submitted to NCAs since January 2013 was requested. The list provided did not include non-marketed products. As a result, it was not possible to confirm that the CAPA relevant to finding C.4.2.b from the 2014 inspection, which related to the implementation of a process ensuring that all relevant safety variations had been approved and updated PILs implemented into packs prior to product launch, was effective.

vi. As per request [redacted] (requested on 08 December 2015), a list of products which were handled by Kohne Pharma GmbH was requested. The documentation in relation to this request was not provided until the final day of the inspection (10 December 2015). The list provided did not include products [redacted]

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vii. As per request [redacted] (requested on 09 December 2015), in order to confirm compliance with case processing and reporting requirements, a listing of invalid cases was requested from the MAH. The MAH was asked to provide the reason why these cases were considered invalid and dates of follow-up attempts. The listing provided did not include this information.

It was not possible to reconcile the listing provided with invalid cases identified by the inspectors. For example, [redacted] relating to an adverse event experienced with [redacted] was identified. This was received by the MAH in July 2014 from a [redacted] This case could not be found in the line listing provided.

viii. Request [redacted] a list of products previously handled by Kohne Pharma and [redacted] a project plan of Cipla (UK) Ltd data migrated to the Cipla Ltd DSD pharmacovigilance database, were requested on the morning of 08 December 2016. However responses to these documents were not provided until the morning of 10 December 2015. It is the MHRA's expectation that such documents would have been readily available.

Root Cause Analysis

[redacted]

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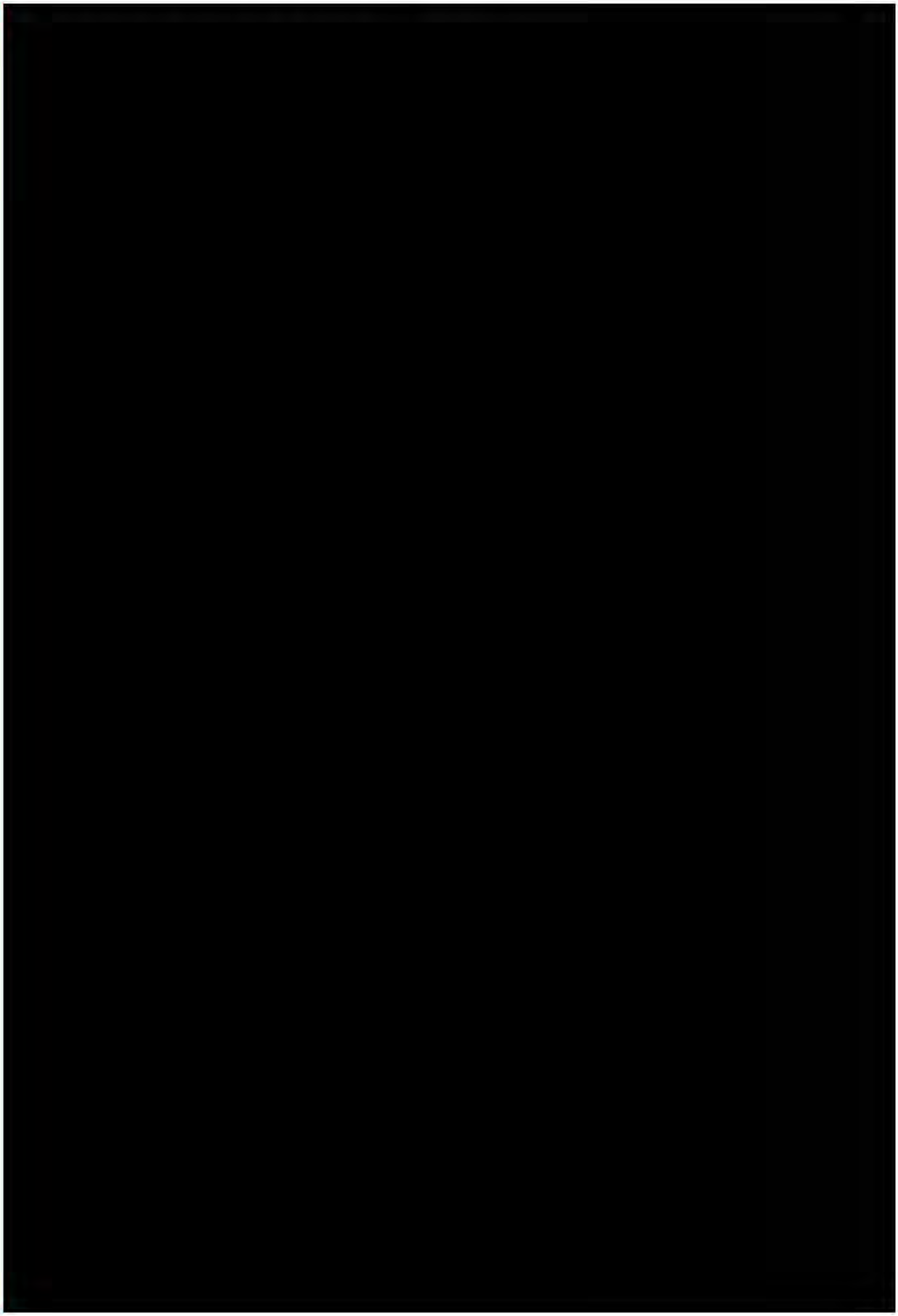

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

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[redacted]

Preventative Action(s)
[redacted]

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

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[redacted]

Finding CR.2 c)

The inspectors were unable to confirm corrective reporting to rectify an absence of reporting of third country ICSRs (as part of the CAPA for finding C.4.1 b from the 2014 inspection, due to the inadequacies of the data provided (see finding CR.2 b). In an explanation provided by the MAH on 22 December 2015 for low case numbers and reporting (the response provided to document request [redacted], the MAH indicated that only serious third country ICSRs which were not listed in the local product information were expedited to EU Competent Authorities.

The MAH is reminded that all serious spontaneous ICSRs, irrespective of listedness, must be submitted to Eudravigilance and specific member states according to the arrangements indicted in GVP Module VI, Management and reporting of adverse reactions to medicinal products and the Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

C.4.2 Major findings

MA.1 Management and Reporting of Adverse Reactions

Requirements:

Directive 2001/83/EC as amended, Article 107.

"1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post authorisation study. […]

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals."

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulations 187-188.

Commission Implementing Regulation (EU) No. 520/2012, Chapter V.

GVP Module VI – Management and reporting of adverse reactions to medicinal products.

The following findings were noted in relation to management and reporting of adverse reactions:

Finding MA.1 a)

There were deficiencies in the handling of pregnancy exposure cases with no associated adverse events. The inspectors were unable to verify if all cases were recorded appropriately. The following deficiencies were noted;

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i. The MAH was unable to provide listings of pregnancy exposure cases without adverse events. These cases were defined as invalid as per Cipla Ltd SOP [redacted] however, the invalid case list provided did not capture event terms.

ii. The ARGUS data prior to 2015 appeared to contain an implausibly small number of cases where there was "Exposure during pregnancy" but no other associated adverse events. According to document request I7 (Line listing of cases in ARGUS database from 2011), there were no cases of "Exposure during pregnancy" without associated adverse events up to 2015, but in 2015 to the time of inspection there were approximately 50 of such cases.

iii. The [redacted] Procedure for Call Handling for Cipla

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[redacted] did not include instructions for the recording of pregnancy exposure cases.

iv. In the [redacted] Assessment and Processing of Adverse Drug Experiences/Events received from Post-marketing Source, versions 6-8, effective from November 2014 to the date of inspection, section 1.5.2.11 included "drug exposure during pregnancy with no AE" in the description of "invalid" cases. Section 1.5.2.1.3 stated that "During PSUR Line listing or any other safety data generation, invalid cases should be excluded". Since 'invalid' cases included drug exposure during pregnancy with no AE (section 1.5.2.11), this is not an appropriate exclusion.

Root Cause Analysis

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[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

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[redacted]

Finding MA.1 b)
The MAH did not have a mechanism in place to collect adverse drug reaction reports from National Competent Authorities other than the MHRA (e.g. BfArM, Germany, Health Canada and the Therapeutic Goods Administration, Australia).
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 c)

Cipla Ltd DSD staff members [redacted] and [redacted] who were responsible to reviewing the email mailbox [redacted] and identifying AEs, as well as forwarding them to drug safety for case processing, did not have any records of pharmacovigilance training.

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

Deficiencies in the area of reconciliation of adverse events between Cipla DSD and partners were observed.

- As per the corrective action of finding C4.1 f of the 2014 inspection report, retrospective reconciliation of adverse events was due to take place between Cipla and [redacted] by 31 August 2015. However, this did not take place until 30 Nov 2015.

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- There was no evidence of reconciliation of adverse events between Cipla and [redacted] despite an SDEA being in place since 19 January 2015 and a provision in the SDEA requiring quarterly reconciliation.
- There was no evidence of reconciliation of retrospective adverse events between Cipla and Aurobindo despite an SDEA being in place since 03 October 2013 and a provision in the SDEA requiring monthly reconciliation.
- The multiparte agreement between APCER, Cipla Ltd and S&D Pharma [redacted] stated that reconciliation of adverse events took place on a monthly basis between all parties. There was no evidence of reconciliation covering periods between 01 February 2015 and 30 September 2015.

Root Cause Analysis

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Further Assessment

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Corrective Action(s)

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

Preventative Action(s)

[redacted]

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

MA.2 Control and Maintenance of Reference Safety Information

Requirements:

Directive 2001/83/EC as amended, Paragraph 40, Article 23 (3) and Article 93 (2).

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

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 summaries of product characteristics (SPCs) and patient information leaflets (PILs) so that healthcare professionals and patients are able to use the medicinal product correctly on the basis of full and comprehensive information.

The finding in relation to the control and maintenance of reference safety information from the 2014 inspection was not resolved.

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Finding MA.2 a)

The procedures for maintaining SmPCs were not adequate in that:

i. As part of the preventative action for finding C4.3 a of the 2014 inspection, the MAH committed to undertaking quarterly comparisons of the MAH's product information with reference (innovator) product information. However, according to SOP [redacted] Handling of Urgent Safety restrictions and safety variations [redacted] comparisons take place annually.

ii. The SOP was not sufficiently detailed in describing the start dates for measuring timeliness of submissions (the tracker does not include dates when innovator comparisons were actually undertaken).

iii. On review of the [redacted] submission, made in June 2015, the comparison vs the innovator SmPC of September 2014 was listed as 'requested' in January 2015, with no record to indicate when the review was actually conducted, inconsistent with quarterly reviews.

iv. There was no written procedure to adequately describe in detail the actions to address the previous inspection finding action (to ensure that release of product cannot occur prior to incorporation of the latest approved PIL).

Root Cause Analysis

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[redacted]

Corrective Action(s)

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

Preventative Action(s)

[redacted]

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[redacted]

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

MA.3 Signal Management

Requirements:

Directive 2001/83/EC as amended, Article 104 (2) (3(e)).

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 182 and 190.

Commission Implementing Regulation (EU) No. 520/2012, Article 21 (1).

GVP Module IX – Signal management.

Marketing Authorisation Holders are obliged to ensure that information on the benefits and risks of their products is evaluated on an ongoing basis, and appropriate action is taken in response to new information that impacts on the benefit-risk balance.

At the time of the inspection the MAH was not meeting this obligation as it did not have the appropriate mechanisms and systems in place to allow for adequate signal generation and trend analysis. The following findings were noted in relation to signal management:

Finding MA.3 a)

Signal detection activities were not conducted based on data from all appropriate sources.

i. There was no evidence that adverse events from the Cipla Ltd (DSD) ARGUS global safety database were considered during safety reviews.
ii. There was no evidence that adverse events which were deemed to be invalid reports were considered during safety reviews. At the time of inspection, there were approximately 150 cases which had been deemed invalid.
iii. Adverse events for products with active substances held by the Cipla group of companies (e.g [redacted]e) contained on the safety database managed by Kohne Pharma GmbH (see finding CR.1 c)), were not considered during safety reviews.

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[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

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[redacted]

Preventative Action(s)

[redacted]

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

Finding MA.3 b)

As part of the corrective actions for finding C4.3a of the 2014 inspection, the MAH committed to undertaking drug safety reviews (DSRs) for drug event pairs (listed below) by 15 December 2014. The DSRs were not undertaken as per the agreed time line and in one case this resulted in a delay of labelling updates being made;

i. The DSR for the drug event term [redacted] and acute chronic renal failure was not approved by the QPPV until 25 June 2015. The DSR resulted in a proposed update to product information. There was no evidence that the associated safety variation had been submitted to NCAs at the time of the inspection and it did not appear on the safety variation tracker.
ii. The DSR for the drug event term [redacted] and acute/chronic renal failure was not signed by the QPPV until 08 December 2015, day one of the inspection.
iii. The DSR for [redacted] was not signed by the QPPV until 01 October 2015.

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[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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[redacted]

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

Finding MA.3 c)

As per the corrective action relating to finding C4.3 a of the 2014 inspection, the MAH committed to conducting a review of events previously identified as potential signals. This was due to a finding that signals that were listed on a tracking spreadsheet were not evaluated in a timely and appropriate manner. Examples were identified during this inspection where there was a continued delay in signal validation, with many signals being validated until the week prior to the inspection and some signals taking over three years to validate.

Product	Signal	Date Identified	Date Validated	Time Taken to Validate (Months)
[redacted]	Sjogren's syndrome	[redacted]	[redacted]5	26.5
[redacted]	Pancreatitis	[redacted]	[redacted]	47
[redacted]	Bile duct syndrome	[redacted]	[redacted]	22.5
[redacted]	Vanishing bile duct syndrome	[redacted]	[redacted]	33.5
[redacted]	Fixed drug eruption	[redacted]	[redacted]	51
[redacted]	Intracranial haemorrhage	[redacted]	[redacted]	48

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[redacted]

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[redacted]

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[redacted]

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[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

MA.4 Quality Management System

Requirements:

Directive 2001/83/EC as amended, Article 108 (b).

Commission Implementing Regulation (EU) No. 520/2012, Chapter II.

GVP Module I – Pharmacovigilance systems and their quality systems.

GVP Module IV – Pharmacovigilance audits.

Deficiencies in the area of quality assurance auditing were identified at the previous inspection. Deficiencies remained in this area with risk-based audit planning not having adequate coverage of the global pharmacovigilance system. Due to time constraints, the area of Quality Management System area was not covered in sufficient detail during this inspection and it is recommended that this area is covered at the next inspection of the MAH. The following findings were noted in relation to the quality management system:

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Finding MA.4 a)

As per the corrective action in finding C4.1 f of the 2014 inspection report, an Audit Management Plan was due to be implemented on 30 June 2015 (DSD-03-001). This plan was not signed off until 18 August 2015, and remained deficient in that risk based audit assessment did not include partners from Europe and North America or global Cipla affiliate offices. Due to the level of missing information from the PSMF in relation to the sources of safety data, the MAH should consider if any other sources of safety data are missing from the risk based audit assessment.

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[redacted]

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[redacted]

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[redacted]

Corrective Action(s)

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

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[redacted]

Preventative Action(s)

[redacted]

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

Finding MA.4 b)

Examples were identified where the MAH failed to implement CAPAs from the previous inspection. Details are outlined below;

- The CAPA for finding C.4.1 of the 2014 inspection (failure to implement an integrated safety database which held pharmacovigilance data from all Cipla subsidiaries) was not fully implemented. A key component of this CAPA was the implementation of an integrated safety database by 30 June 2015, however at the time of the inspection this action was outstanding (see finding CR.1 a) in this inspection report).
- The CAPA for finding C4.1b of the 2014 inspection (failure to report third country ICSRs to Eudravigilance and relevant EU NCAs) was not implemented at the time of inspection (see finding CR.2 d) in this inspection report). Serious third country ICSRs which were listed in local product information were not being reported to Eudravigilance and relevant EU NCAs.
- The CAPA for finding C4.3a of the 2014 inspection (control and maintenance of reference safety information) was not fully implemented, with the preventative action to undertake quarterly comparisons of the MAH's product information with the reference (innovator) product information not taking place (see finding MA.3 a) of this inspection report).

Root Cause Analysis

[redacted]

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[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.

D.2 Recommendations

- This inspection report will be shared with pharmacovigilance inspectors from SÚKL (Czech NCA). This is because Cipla (UK) Ltd has a QPPV and PSMF based in the Czech Republic, and the Czech pharmacovigilance inspectorate may wish to take the outcome of this inspection into account when preparing their inspection schedule.
- As it was not possible to inspect the compliance of pharmacovigilance for clinical trials/study activity during this inspection, it is recommended that this area will be inspected at the next inspection of Cipla.
- It is recommended that the implementation of the most up-to-date PILs in product pack should be reviewed at the next inspection, as this was not fully examined during this inspection due to missing information from document requests provided to inspectors (see finding CR.2 b) v).
- Due to the critical inspection finding, the inspection was referred to the Inspection Action Group for GCP and Pharmacovigilance (IAG). In order to evaluate the implementation and effectiveness of the CAPA proposed by Cipla in response to these inspection findings, it is likely that the next MHRA inspection will be performed within 12 to 18 months post the date of the last inspection.

APPENDIX I REFERENCE TEXTS

- 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) Modules.
- Directives 2001/20/EC and 2005/28/EC in relation to Clinical Trials.
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/287/95: E2B (M) "Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports" and ICH E2B(R2) "Maintenance of the Clinical Safety Data Management: Data Elements For Transmission Of Individual Case Safety Reports".
- EMA/CHMP/ICH/544553/1998: E2C (R2) "Periodic benefit-risk evaluation report (PBRER)".
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- CHMP/ICH/309348/2008: E2F "Development safety update reports".
- CPMP/ICH/135/95: E6 (R1) "Guideline for Good Clinical Practice".
- Eudralex Volume 10, Chapter II: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT3'), June 2011.
- CHMP/313666/05: "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	08 December 2015
LOCATION	C/O APCER Pharma (Europe) Ltd, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL	**START TIME**	10:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting • review of scope of inspection and inspection plan • presentation by Cipla regarding the status of CAPAs from the last inspection and a summary of any additional key changes to the pharmacovigilance system	[redacted]	All welcome
Migration of data from APCER and S&D Pharma databases to ARGUS database	[redacted]	Interviewee(s):
LUNCH	-	-
Review of processing, follow-up and submission of adverse reaction reports including;* • submission of third country ICSRs • clinical trials • use of non-EU data in PSUR production • literature searching and review *Please note: A separate ad-hoc session in relation to this area may be requested at another time during the inspection.	[redacted]	Interviewee(s):
Document Review	-	Inspectors Only

N.B.
Relevant SOPs, working practices, training records, CVs and job descriptions should be made available to the inspection team.
Other documents will be requested during the inspection.
The Inspection Plan may need to be amended during the inspection.

[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	09 December 2015
LOCATION	C/O APCER Pharma (Europe) Ltd, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Ongoing safety monitoring/signal detection activities	[redacted]	Interviewee(s):
Document Review		Inspectors only
LUNCH		-
Maintenance of reference safety information, including core safety information, SPCs, PILs		Interviewee(s):
Pharmacovigilance Agreements, including • Set up and management of SDEAs • Reconciliation of safety data		Interviewee(s):
Document Review		Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	10 December 2015
LOCATION	C/O APCER Pharma (Europe) Ltd, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Quality Management System • auditing of pharmacovigilance activities conducted by CIPLA and APCER • CAPA management *Due to time constraints, this session was not covered in great detail.*	[redacted]	Interviewee(s):
Document review	-	Inspectors only
LUNCH	-	-
Roles and responsibilities of EU/EEA Qualified Person	[redacted]	Interviewee(s):
Document review		Inspectors Only
Closing meeting		All welcome