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 36390/1480807-0003

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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

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Inspection type:	Re-inspection
Name and address(es) of site(s) inspected:	Cipla (EU) Ltd C/O APCER LS, 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]
Date(s) of inspection:	Office based inspection (at the offices of the MHRA): 02 and 03 May 2017 On-site inspection (at the offices of APCER LS): 08 – 12 May 2017
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted]
Previous inspection date(s):	08 – 10 Dec 2015 24 – 26 Jun 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] (until 11 Sept 2017) Contact details as above From 11 Sept 2017: [redacted] 346 Kensington High Street, Kensington, London W14 8NS, UK [redacted]
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 LS (EU-

	QPPV, global safety database maintenance, PSUR writing, signal detection).
Inspection finding summary:	3 major findings 5 minor findings
Date of first issue of report to MAH	07 Jul 2017
Deadline for submission of responses by MAH	11 Aug 2017
Date(s) of receipt of responses from MAH	11 Aug 2017, 01 Sept 2017, 19 Dec 2017 (following a meeting at MHRA 29 Nov 2017)
Date of final version of report	20 December 2017
Report author	[redacted]
Responses reviewed by	

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Cipla (EU) Ltd was selected for re-inspection as a result of two critical findings that were identified during the previous re-inspection of the Marketing Authorisation Holder (MAH), performed on 08 - 10 Dec 2015. 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 d.o.o. 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, Cipla NV, Cipla Croatia and Cipla (UK) Ltd including QPPV services, are outsourced to APCER LS. 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. With the exception of literature monitoring, all of these activities were limited to safety information originating within the EEA.

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 and literature monitoring.

B.2 Scope of the inspection

The inspection focussed on a review of the systems and processes which were associated with critical and major findings reported at the previous inspection.

The inspection was performed remotely at the offices of the MHRA in Buckingham Palace Road, London (02 - 03 May 2017) and on-site at the offices of the pharmacovigilance service provider APCER LS, in Ealing, Greater London (08 – 12 May 2017). Personnel from Cipla and APCER attended the Ealing site in order to participate in the inspection.

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. Various document requests (as outlined in pre-inspection document request sheet A) were made and provided to the inspection tram in preparation for the inspection, including; safety data exchange agreements (SDEAs), SOPs, line listings of all worldwide case reports and invalid cases, various data migration and project plans and information on safety variations submitted to the MHRA.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan (attached as Appendix II). Due to the unavailability of an inspector on day three, the order of some interview sessions changed (as indicated in Appendix II). A number of ad hoc interview sessions were conducted as required.

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, Ealing on 12 May 2017. 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:

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- Multiple data migrations were undertaken, including the migration of pharmacovigilance data held by [redacted] and Cipla Med Pro (South Africa) to the Cipla DSD managed Argus database.
- The migration of pharmacovigilance data from the Apcer managed ARISg safety database (containing all Cipla EU originating cases as well as some non-EU originating cases requiring reporting to a European NCA) to the Cipla DSD managed Argus safety database.
- There was a major restructuring of the DSD and various changes in pharmacovigilance staff, including the appointment of a new DSD Head for Cipla.
- Cipla acquired two US based companies [redacted] does not hold MAs).
- The responsibility for the maintenance and control of the PSMF was moved from APCER LS to Cipla DSD.
- Pharmacovigilance activities for Cipla (UK) Ltd was previously undertaken by the service provider S&D Pharma. These activities have now been moved to Apcer LS.

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

Two critical findings were reported at the 2015 pharmacovigilance inspection of Cipla.

- CR.1 - Failure to establish a global pharmacovigilance system. This finding was initially reported at the 2014 pharmacovigilance inspection of Cipla. At the 2015 re-inspection of Cipla, this finding had not been sufficiently resolved and therefore remained a critical deficiency. The outstanding deficiency related to pharmacovigilance data for common active substances being recorded in multiple pharmacovigilance databases, with not all sources being accessed during PSUR production and signal detection activities. The finding was considered to have been partially resolved at the 2017 pharmacovigilance inspection, as Cipla had taken steps to migrate pharmacovigilance data to a single pharmacovigilance system, and this data was made available for the purposes of signal detection and PSUR production. The finding was no longer regarded as a critical deficiency. A major finding was reported in relation to the data migration of pharmacovigilance data (see finding MA.3) which related to Cipla's efforts to establish a global pharmacovigilance system.
- CR.2 - Pharmacovigilance System Description and Documentation – Supervision and oversight. The failures in provision of documentation to describe the PV system were a significant impediment to the inspection process in 2015, 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. This finding was considered to have been resolved at the 2017 pharmacovigilance inspection, and thus no longer remained a critical deficiency.

No further critical findings were identified at this inspection, and as indicated above, the two critical findings reported at the 2015 inspection (failure to establish a global pharmacovigilance system and pharmacovigilance system description and documentation) were regarded to have been partially addressed, although major findings were reported in those areas.

MA.1 Periodic Safety Update Reports

Requirements:

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

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulations 191, 192.

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

GVP Module VII – Periodic Safety Update Report.

VII.B.2. Principles for the evaluation of the risk-benefit balance within PSURs and scope of the information to be included "The evaluation should involve: [...] 3. Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorisation holder does not have access to data from the clinical development period, the earliest possible applicable date should be used as starting point for the inclusion and evaluation of the cumulative information".

VII.B.3. Principles for the preparation of PSURs "When data received at the marketing authorisation holder from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing authorisation holder's product information, these data should be included and discussed in the PSUR."

VII.B.5.2. PSUR section - Worldwide marketing authorisation status "This section of the PSUR should contain a brief narrative overview including: date of the first authorisation worldwide, indications(s), authorised dose(s), and where authorised".

VII.B.5.5.2. PSUR sub-section - Cumulative and interval patient exposure from marketing experience "Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PSUR)".

VII.B.5.6.3. PSUR sub-section - Cumulative and interval summary tabulations from post-marketing data sources "This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies[10]. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The

table should be organised by MedDRA SOC (listed in the internationally agreed order) […]" (emphasis added).

VII.B.5.15. PSUR section - Overview of signals: new, ongoing, or closed "[…] The purpose of this section is to provide a high level overview of signals[16] that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval".

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PSURs were scheduled, authored, quality checked and submitted by APCER. Cipla provided the source data and reviewed content (this was not understood to be a formal quality check) of the PSURs. Two PSURs were reviewed in detail during the inspection: [redacted] The following findings were noted in relation to PSURs:

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Finding MA.1 a)

Due to availability of data, the data migrations from [redacted] used .xml files which did not contain event level seriousness. The migration strategy employed by Cipla defaulted all event-level seriousness assessments to non-serious, even for cases which were serious at case level. The shortcomings in the migration strategy were noted by Cipla on QPPV review in October 2016 but PSURs were submitted with incorrect event level seriousness in the summary tabulations. Affected PSURs included;

i. [redacted] At the time of inspection the MAH estimated that there were approximately 160 events contained in the cumulative summary tabulations that were classified as non-serious but which would have been serious according to the IME list current at the time of inspection and thus may have required reclassifying as serious (Document request [redacted]. Examples of events classified as non-serious are included in Appendix III.

ii. [redacted] At the time of inspection the MAH estimated that there were approximately two events contained in the cumulative summary tabulations that were classified as non-serious but which would have been serious according to the IME list current at the time of inspection and thus may have required reclassifying as serious. (Document request [redacted]. The two events classified as non-serious included the following:

[redacted] Cellulitis

[redacted] Neutropenic sepsis

It is noted that a remediation plan in was put in place for event level seriousness for [redacted] data and was signed off on 12 Apr 2017 and completed during the inspection This remediation plan involved making all event level seriousness assessments consistent with case level seriousness but that this was only partially successful and a deviation was raised as some serious cases had only one event assessment as serious with others left as non-serious (e.g [redacted].

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

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

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[redacted]

Finding MA.1 b)

Section 2 'Worldwide Marketing Authorisation Status' of the [redacted] PSUR [redacted] states that "currently Cipla (EU) Ltd and its affiliates ([...] [redacted] holds a MA" (for [redacted] in listed territories). This was inaccurate as Cipla was the MAH in the territory where [redacted] acted as a distribution partner and [redacted] were not an affiliate of Cipla. See also finding MI.4 a in relation to [redacted] not being included in Annex B of the PSMF.

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]

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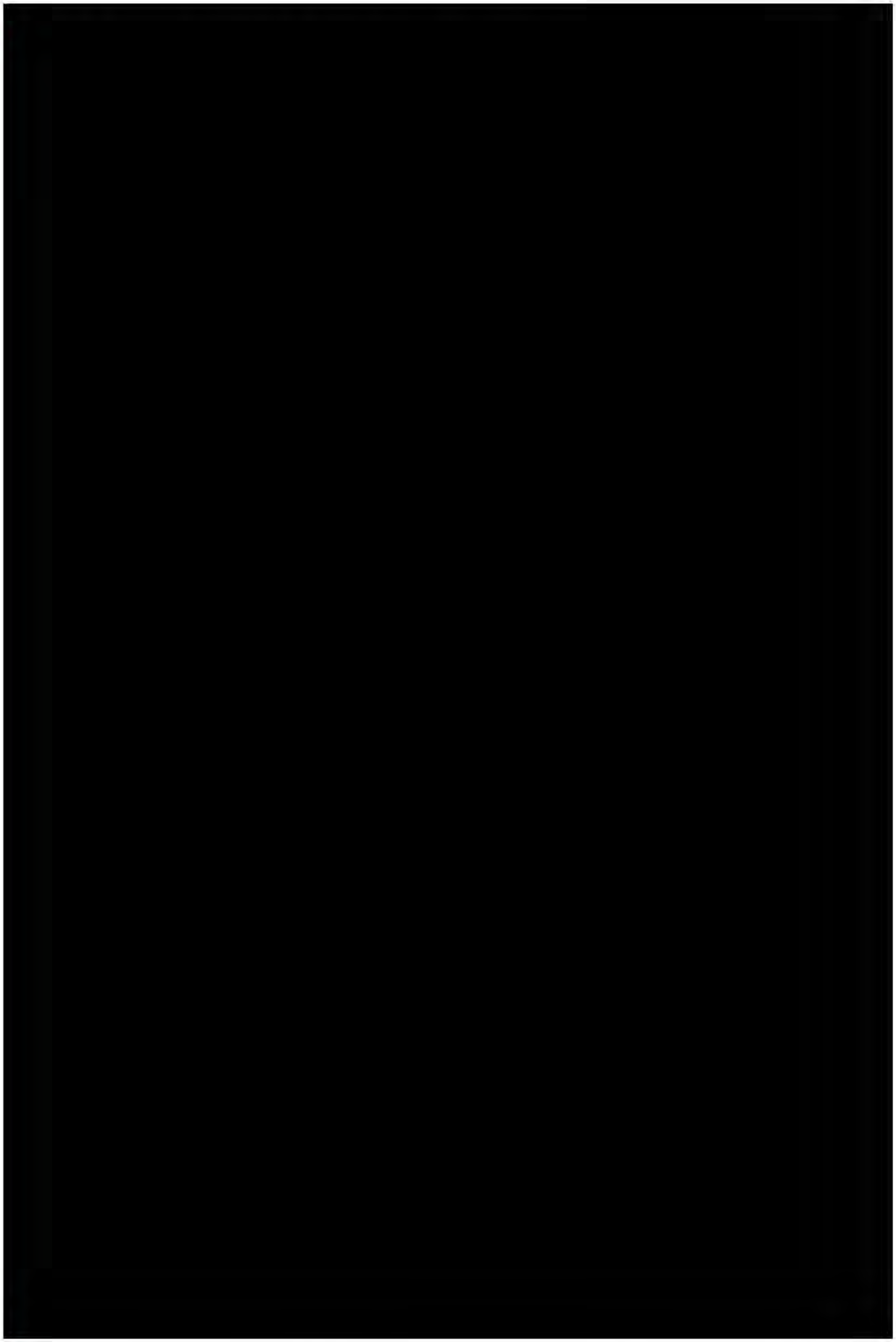

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[redacted]

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[redacted]

Finding MA.1 c)
Data included in the cumulative and interval summary tabulations from post-marketing data sources of the PSURs had the following deficiencies; i. The event of balanoposthitis in case [redacted] with initial receipt date of 10 Nov 2011, was not included in the cumulative listings in the [redacted] PSUR [redacted] despite being received after the international birthdate (IBD) of the product (IBD was 18 Jul 1995 as per the EURD spreadsheet rev. 56). Cipla confirmed this was excluded because the case had a receipt date prior to the

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date of first authorisation of [redacted] in the EU (24 Jan 2012). The case was originally received by Invagen (now acquired by Cipla) and was included in the Cipla global safety database following the migration of Invagen cases. The case therefore had been included as part of the cumulative data set used by Cipla for routine signalling activities. Cipla should assess the impact of this finding on other PSURs.

MHRA request: In accordance with GVP VII B.5.6.3, the PSUR cumulative and interval summary tabulations from post-marketing data sources should contain adverse reactions from the International Birth Date of the product to the DLP of the current PSUR. Cipla are requested to consider the information that has been used to construct PSURs to date considering the information available within the global safety database. Cipla are requested to provide a list of all PSURs submitted from December 2015 to date to the lead inspector/designated contact and confirm that all relevant cumulative data has been included.

ii. In the PSUR for [redacted] section 6.3 stated that cumulative data since 18 Nov 2011 (the EU authorisation date of [redacted] for Cipla) was included. During the inspection, Cipla confirmed that data considered for the summary tabulation was within a date range of 01 Jan 1900 to 31 Dec 2016 to include all safety data available in the database. A cumulative line listing provided to inspectors contained over 700 drug event pairs for [redacted] with an initial receipt date prior to November 2011. A spot check between the fully cumulative listing provided and the cumulative numbers of drug event pairs represented in appendix 4 of the PSUR did not reveal discrepancies or omissions in the data. This indicated that Cipla had included cumulative data in the PSUR, however the statement in section 6.3 incorrectly represented the data included in the PSUR.

Root Cause Analysis

[redacted]

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[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]	

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[redacted]

Finding MA.1 d)
Exposure figures in the PSUR for [redacted] were calculated using dispatch data from the manufacturer to country specific distribution routes instead of actual sales figures. For the example of the UK figures this resulted in overestimated patient exposure figures for the reporting period. The dispatch data used was of 12,970 packs dispatched to the UK, however Cipla confirmed that the actual sales for [redacted] in the UK for the period of 24 Jan 2012 - 18 Jan 2017 was 5,234 packs. Cipla confirmed that for all PSURs that had been compiled since 19 Nov 2016, this method was followed for calculation of patient exposure. PSURs with a DLP after 19 Nov 2016 and submission date (in any EU territory) prior to the inspection included: [redacted]
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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Corrective Action(s)
[redacted]

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

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

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Finding MA.1 e)
Section 15 'Overview of signals: New, ongoing or closed' in the [redacted] PSUR [redacted] did not contain the signal of heatstroke, which was detected on 05 Jan 2017 as per the signal tracker. The signal was also not included in Appendix 5: Tabular summary of safety signals. Cipla confirmed this signal had been "inadvertently missed during email communication to the PSUR Preparation team".
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]

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[redacted]

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

Finding MA.1 f)
The following procedural deficiencies were identified in relation to PSUR preparation; 1. Cipla verbally described that case safety data for PSURs were extracted from the Argus data using SQL searches based on a manually derived selection of drug names based on variations of the PSUR product name. There was no process describing how these permutations would be identified or selected. For the line listings provided for the [redacted] PSUR [redacted] a separate line listing was provided containing an additional case with two serious events reported for suspect drug [redacted] a permutation that had not been included in the original search. Although this case had been identified, it indicates

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that the process for manual selection of product names was not robust on its own, however, it is acknowledged that an ongoing project was anticipated to standardise product names in the global safety database by October 2017 prior to the implementation of Argus version 8.

2. There was no documented QC of the listings provided for PSURs by service provider [redacted] to ensure all relevant cases had been extracted from the database. It was identified during an undocumented QC of the line listing provided for the [redacted] PSUR [redacted] that 8 cases were missing from the line listing the first time it was provided.

3. There was no documented procedure for the manual cleaning of the line listings prior to production of the summary tabulations to remove duplicate events, for example, the [redacted] line listing for the PSUR reporting period was reduced from 7,294 drug/event pairs to 4,695 drug/event pairs following cleaning.

4. There were no written instructions on manual preparation of summary tabulations from the line listings. Furthermore, there was no process to remove un-related cases from the [redacted] PSUR [redacted] summary tabulations of post-marketed data. This was evidenced by the presence of the event of 'sialoadenitis' in the summary tabulations. This event appears in the PSUR line listing only once in the case [redacted] where it is captured as unrelated in both reporter and company causality fields.

See also finding MI.1 c) and MI.2 a) in relation to procedural findings for the extraction of data for line listings and use in signal detection activities.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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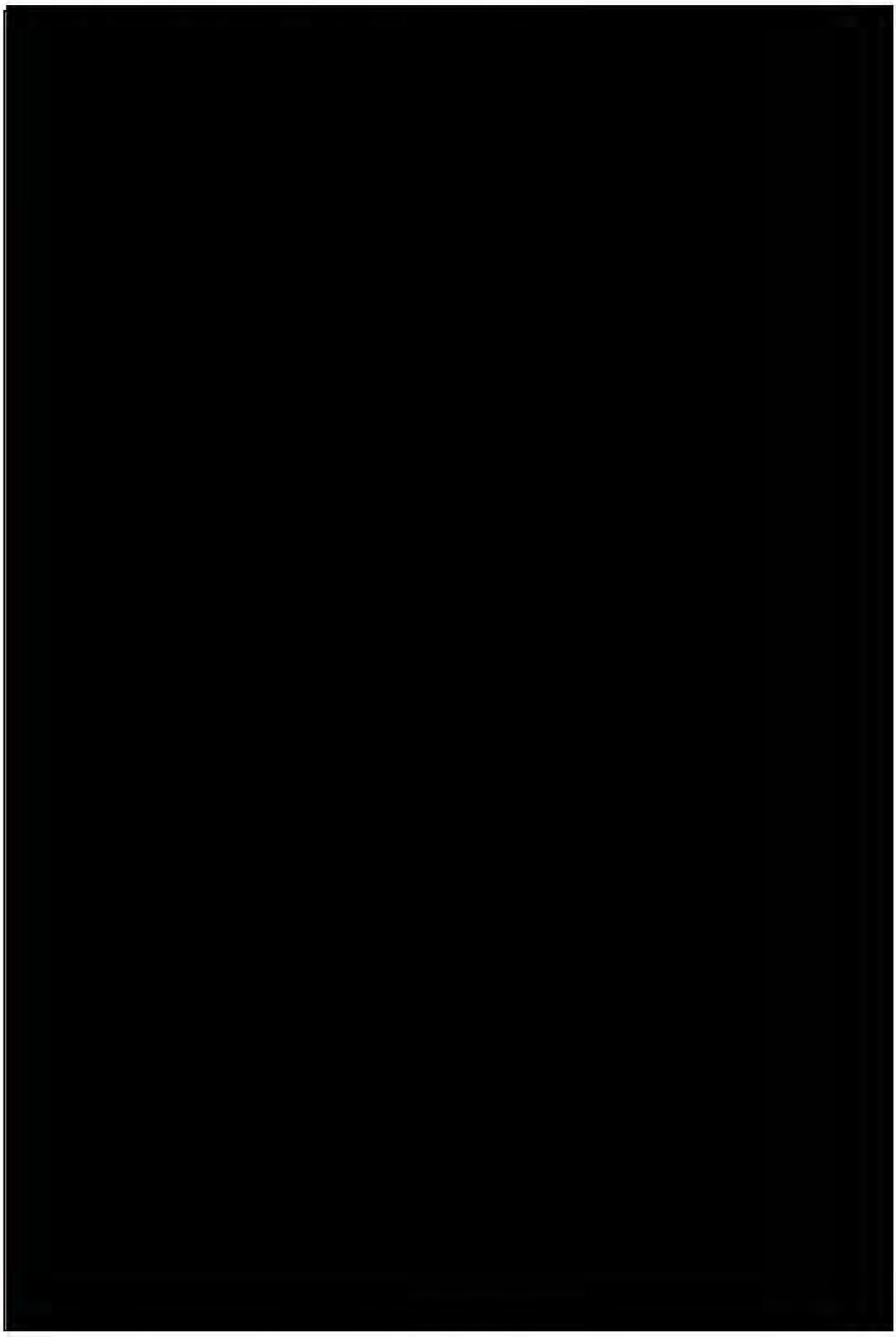

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[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.1 g)

Cipla had three products licenced in the EU via decentralised or mutually recognised procedures for which the licence has been transferred to a partner in certain concerned member states;

- [redacted] the Netherlands
- [redacted] in France
- [redacted] n Portugal.

There was no agreement in place with [redacted] and the agreements in place at the time of the inspection with [redacted] ('License and Supply Agreement between Cipla Limited, Cipla (UK) Limited and [redacted] dated 04 May 2012) and [redacted] ('Supply Agreement (Bulk/Finished packed products)' between Cipla Limited and [redacted] dated 18 Aug 2015) did not allow for exchange of meaningful safety data such as signals or updates to local product information. It should be noted that a PSUR for [redacted] was on the schedule with DLP in May 2017.

It is acknowledged that requests to establish agreements with each of these parties were sent on 26 Jul 2016 with reminders on 19 Oct 2016 and 09 May 2017 to [redacted] and 03 May 2017 to [redacted]

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[redacted]

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Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

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

Comment
[redacted]

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MA.2 Control and Maintenance of Reference Safety Information

Requirements:

Directive 2001/83/EC as amended, Paragraph 40,

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.

Major findings in the control and maintenance of reference safety information were reported at the 2014 and 2015 pharmacovigilance inspections. A finding was reported at the 2015 inspection of deficiencies in the procedures in place to maintain and update product information (finding MA.2 a from the 2015 inspection). This finding had been partially resolved by updating written procedures, however, the MAH commitment to undertake six months comparisons of product information against reference products was not undertaken. Further procedural deficiencies and delays in the submission of safety variations were also identified.

Finding MA.2 a)

A number of delays in the submission of safety variations to the MHRA were identified. The MHRA's expectation is that safety variations would be submitted to the MHRA within six months after the requirement to update product information has been identified by the MAH (or sooner if specifically requested by the MHRA or PRAC/CMDh). These delays also breached the internal Cipla timelines of submitting safety variations within 90 days after identifying that a product information update was required (as outlined in section 2.6.13 - 2.6.16 of SOP [redacted] 'Handling of Urgent safety Restrictions and Safety Variations', [redacted].

Product	Information to be added	Date of identification that product information required updating*	Date of variation submission	Time taken (months, approx.)
[redacted]	Hypotension to section 4.8 of SmPC	25 Nov 2015	23 Feb 2016	15.5
[redacted]	Abdominal pain upper, Headache, Drug abuse, Drug dependence	03 Dec 2015	29 Mar 2017	16

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	and information in relation to serious skin reactions to section 4.8 of SmPC			
[redacted]	Addition of renal failure to section 4.8 of SmPC	12 December 2014	18 Aug 2016	20
[redacted]	Addition of myocardial infarction to section 4.8 of the SmPC	09 Oct 2015	20 Mar 2017	17
[redacted]	Addition of toxic acute hepatitis	07 Dec 2015	08 Apr 2017	16
[redacted]	Addition of fixed drug eruptions	09 Oct 2015	10 Apr 2017	18

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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

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Finding MA.2 b)

As part of preventative actions for finding C.4.3 a from the 2014 inspection, Cipla committed to undertaking a quarterly comparison of the MAH's product information with reference product information. At the 2015 inspection of Cipla, it was identified that the frequency for this comparison to take place had been amended to an annual basis (as per SOP [redacted] Handling of Urgent Safety restrictions and safety variations, [redacted] without any appropriate assessment or justification for choosing this frequency (finding MA.2 a). As part of the corrective action for the finding, Cipla committed to undertaking a comparison of Cipla's product information with reference product information every six months after 30 Apr 2016 and updating the associated SOP. Hence, the first reference product comparison for all products was due to take place by August 2016 at the latest. It was identified that this comparison was not taking place on a six monthly basis for a number of products (for example the comparison of [redacted] and [redacted] did not take place until April 2017).

While the SOP was initially amended to state a six monthly frequency for the comparison as per the CAPA, the SOP was subsequently amended to state an annual frequency for comparison (SOP [redacted]. There was no assessment undertaken to justify changing the frequency of the comparison to an annual basis.

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]

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[redacted]

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

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Finding MA.2 c)

Cipla described a process whereby following the approval of a safety variation resulting in updates to the PIL, batches would not be released later than six months post variation approval with the previous version of the PIL. It was noted that in March 2017, Cipla had identified four products where batches had been released to the UK market with PILs which did not include all of the currently approved information.* Cipla liaised with the MHRA GMP Inspectorate and the Defective Medicines Report Centre on 03 Mar 2017 reporting the issue. For three of the products [redacted] it was agreed with the MHRA that a voluntary recall would take place at wholesale level to withdraw affected batches. Cipla raised a deviation in relation to this issue [redacted] undertook an internal investigation (investigation summary dated 16 Mar 2017) and a CAPA was agreed to be implemented (reference: [redacted] CAPA created 30 Mar 2017, CAPA due date 29 Sep 2017).

Despite this activity having taken place, a further example was identified by the inspectors where a batch of product had been released with an out of date PIL [redacted]. The safety variation had been approved on 28 Jul 2016, however, a batch had been released with the previous version of the PIL approximately eight months after the safety variation approval (batch released in March 2017). The information which was missing from the PIL of safety relevance was the rewording of the terminology used to describe very serious skin reactions under section 4 (Possible side effects). The inspectors did not regard this discrepancy had an impact on patient safety.

*The affected products were [redacted]

Note: At the time of the inspection the written instructions did not define the six month time frame for which batches would not be released with the previous version of the PIL post safety variation approval. It is acknowledged that this was identified as part of the investigation summary relating to the aforementioned deviation, and a preventative action included updating SOP [redacted] with associated timeframes.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[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]	

MA.3 Migration of Pharmacovigilance Data

Requirements:

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

GVP Module I – Pharmacovigilance systems and their quality systems.

I.B.10 Record Management "The organisation shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information. […]The record management system should support: • the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity […]".

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

VI.B.4 – Data management "procedures should be implemented to ensure security and non-corruption of data during data transfer".

VI.B.5 – Quality Management "[…]marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving" (emphasis added).

A critical finding was reported at the 2014 inspection due to the failure of Cipla to establish a global pharmacovigilance system. At the 2015 re-inspection of Cipla, it was deemed that this finding had not been sufficiently resolved and therefore remained a critical deficiency. The outstanding deficiency related to pharmacovigilance data for common active substances being recorded in multiple pharmacovigilance databases. Not all sources being accessed for the purposes of PSUR production and signal detection. At the time of the inspection, Cipla had taken steps to migrate pharmacovigilance data to a single safety database (Argus global safety database managed by Cipla DSD), hence a critical deficiency did not remain. Deficiencies in relation to data migrations were identified which has been graded as a major finding.

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Finding MA.3 a)

i. For the data migrations from the Invagen and [redacted] data bases to the Cipla Argus database, which contained 1,057 cases and 340 cases respectively, both of these migrations were carried out by means of manual data entry, with only data fields that were present on MedWatch forms being entered into the target Cipla Argus database. Additional data available in the source documentation was not migrated. It was noted that the data migration plans for both data migrations (Invagen and [redacted] plans dated 06 May 2016), specified that cases would be entered on the basis of source documents and it was not specified that this would be limited to data

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fields contained in MedWatch reports. Examples included the following:

Case ID	Data field	Source document	As captured in Argus
[redacted]	Event outcome	Ongoing	Unknown
[redacted]	Event severity severe	Severe	Not captured
[redacted]	Dechallenge	Positive	Unknown
[redacted]	Outcome	Resolved	Unknown
[redacted]	Action taken with suspect drug	No action	Unknown
[redacted]	Outcome	Not resolved	Unknown
[redacted]	Action taken with suspect drug	No action	Unknown

ii. The Invagen and [redacted] data migration each had a post-migration QC check of 10% of cases was performed and it was noted by the inspection team that each sample contained a significant numbers of major errors. However this error rate was not fully investigated or escalated. During the inspection when this error rate was highlighted by the inspection team it was found that the high error rate was the result of the data entry during the migration being performed using MedWatch forms and not the full source documentation.

During the 2017 inspection, Cipla committed to full re-entry of all the Invagen and Medpro cases.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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

C.4.3 Minor findings

MI.1 Management and Reporting of Adverse Reactions

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Finding MI.1 a)
There were six examples of cases which were classified as non-serious but which contained serious events. All appeared to have been caused by data entry errors e.g. [redacted] was processed as a serious case in the data entry workflow but inadvertently had seriousness changed from serious to non-serious in the case summary tab. This error was not identified by the quality reviewer or the medical reviewer. Case affected were as follows; [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]

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[redacted]

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

Finding MI.1 b)

SOP [redacted] Recording & Reporting of AEs & SAEs in Post Marketing Non Interventional Studies [redacted] did not stipulate collection of reports of pregnancy other special situations apart from adverse events. It is acknowledged that there was a draft procedural document at the time of the inspection that contained this missing information. It is also acknowledged that training material used to train PSP vendors included reference to pregnancy reports.

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]	

Finding MI.1 c)
i. Incorrect data listings were supplied to inspection team. The event level data listing supplied to inspectors as part of the pre-inspection requests (document request [redacted] was incorrect and showed incorrect event level seriousness. In the line listing provided (document request [redacted] drug event level format) a join was made between the product table and the event assessment table using Case ID as a common field. At this step the join should have also used the event preferred term as a common field however this was missed with the result that every preferred term was reported

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against every permutation of event level seriousness within the case. Cipla were able to supply a corrected listing during the inspection, however, the provision of inaccurate line listings was also reported at the 2015 inspection (finding CR.2.b).

ii. There were no written procedures in place to ensure quality control of ad-hoc line listings obtained from the database. It is acknowledged that a document was in draft.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)

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[redacted]

Finding MI.1 d)

The SDEA between Cipla and [redacted] (distributor of Cipla product in [redacted] livery) was signed on 28 Apr 2017, despite commercial activities commencing with [redacted] since January 2017.

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]

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[redacted]

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

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MI.2 Signal Management

Signal detection was performed by Cipla on a six-monthly basis on a cumulative output from the global safety database. At the 2015 inspection, a major finding was reported in the area of signal management. The CAPA from the MHRA GPvP inspection in 2015 had been met in that a review of previously identified signals had been performed and signal detection had been performed on the global safety data set. A review of the signal detection process implemented per Cipla SOP [redacted] 'Signal Detection and Risk Management' [redacted] on a cumulative output for all products from the global safety database (Argus) with a data lock point of 31 December 2016 was performed by the inspectors and the following deficiencies were identified with the written instructions for this process:

Finding MI.2 a)
The SOP [redacted] described that the cumulative line listing would undergo cleaning prior to application of statistical tools for signal detection. The SOP stated that the cleaning would apply uniform product names and remove duplicate and cluster cases from the listing. For the data used in the signal detection on cumulative data with a DLP [redacted] Dec 2016, the clean-up resulted in the removal of 317,262 drug/event pairs from the cumulative listing generated from Argus (601,397 total drug/event pairs reduced to 284,135). There were no detailed instructions on how this process would be performed and for example how duplicate and cluster cases would be identified for removal, particularly for cases migrated from ARISg, where cluster cases could only be identified manually. Furthermore, there was no process for quality control of the 'cleaned' listings prior to application of statistical tools (see also finding MA.1 f in relation to procedural deficiencies in relation to the extraction of data for inclusion in PSURs).
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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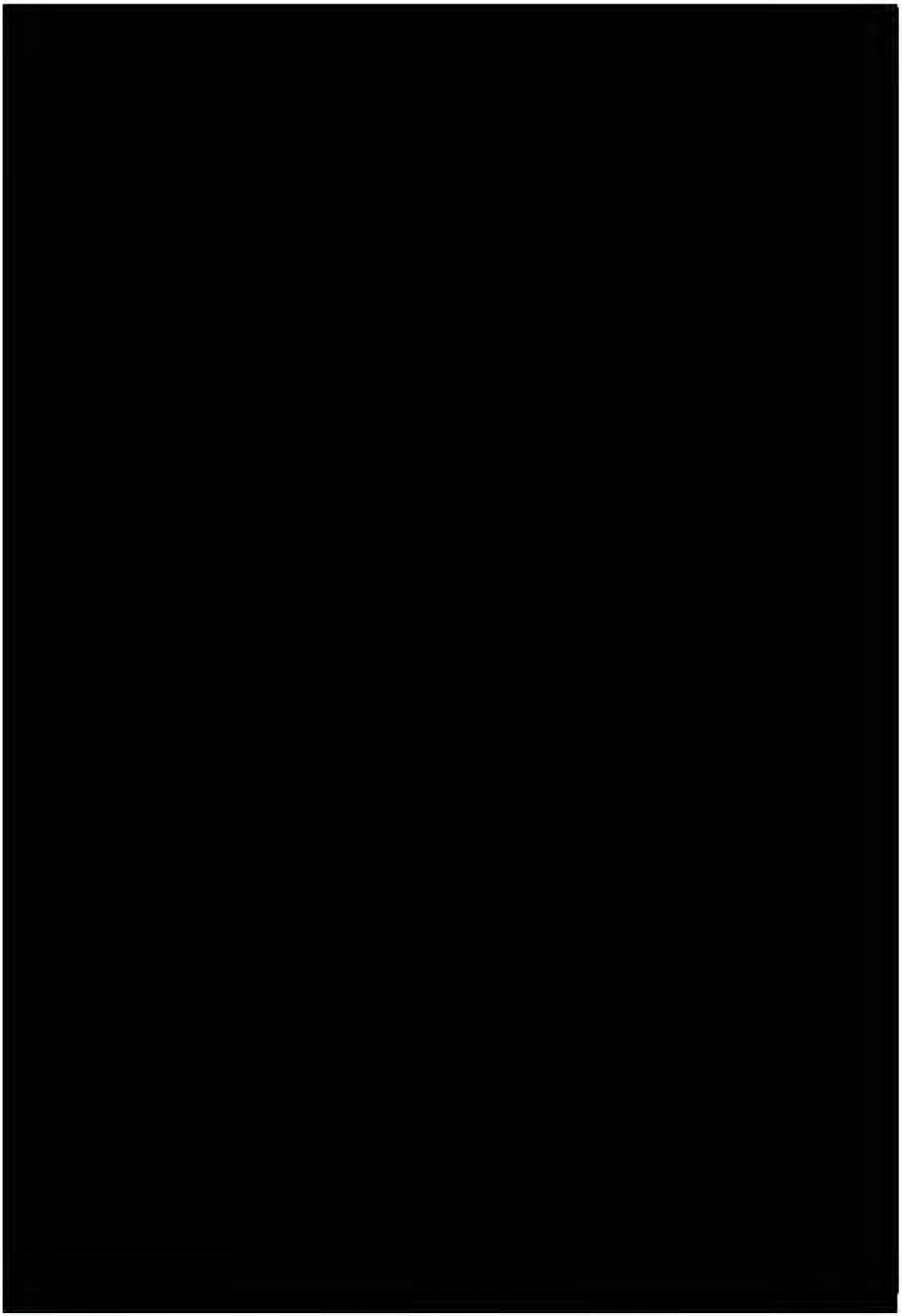

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[redacted]

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]	

MI.3 Auditing of the Pharmacovigilance System

A major finding was reported at the 2015 inspection as the risk-based audit planning did not have adequate coverage of the global pharmacovigilance system. This finding was deemed have been sufficiently resolved at the 2017 inspection, with the following minor finding being reported.

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Finding MI.3 a)
[redacted] were responsible for distributing Cipla licensed product in South Africa (pharmacovigilance agreement signed since July 2011). This entity was not included in the risk-assessment undertaken to prepare the 2016 and 2017 tactical audit plan.
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]

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[redacted]

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

MI.4 Pharmacovigilance System Master File

A component of the critical finding reported at the 2015 pharmacovigilance inspection related to deficiencies in the accuracy of the PSMF (CR.2). Deficiencies in relation to the accuracy of the PSMF had been resolved with the following minor finding being reported.

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Finding MI.4 a)
[redacted] were responsible for distributing Cipla licensed product in South Africa (pharmacovigilance agreement signed since July 2011). [redacted] was not included in Annex B (list of business partners) of the PSMF [redacted]
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]

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[redacted]

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

MI.5 Data Provided to Inspectors

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Finding MI.5 a)
Inaccuracies were observed in the sales figures covering the year prior to the inspection provided in response to document request [redacted] The figures stated that there were 81,474 packs (10 mg) and 36,805 packs (20 mg) of [redacted] sold in the EU during the year prior to the inspection, however, it was confirmed to the inspectors that there was no [redacted] marketed in the EU during that period.
Root Cause Analysis
[redacted]
Further Assessment
[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 to consider whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

During review of proposed responses to these inspection findings, the inspection was referred via the MHRA GPvP inspectorate Compliance Management Team (CMT) to the MHRA Inspection Action Group for GCP and Pharmacovigilance (IAG2). A meeting was held at the offices of the MHRA on 29 November 2017 to outline the concerns the lead inspector had regarding the inspection responses.

The updated responses following the meeting, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. The MAH has agreed to provide the lead inspector with the requested summary of the outcome from the Master Business Partner Reconciliation project and a summary from the PSUR review project, as detailed in the responses to the inspection findings. 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

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[redacted]

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

There were changes to the order of interview sessions on day three and four. See amendments in red and strikethrough.

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	02 May 2017
LOCATION	Office based inspection day MHRA Offices, Buckingham Palace Road.	**START TIME**	09:30

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review and ad hoc questions	-	MAH representatives will be contacted on an ad hoc basis if required

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**	03 May 2017
LOCATION	Office based inspection day MHRA Offices, Buckingham Palace Road.	**START TIME**	09:00
Purpose of Interview	**Session Lead**	**Staff to be interviewed**	
Document review and ad hoc questions	-	MAH representatives will be contacted on an ad hoc basis if required	

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	08 May 2017
LOCATION	APCER offices, C.P. House, 97-107 Uxbridge Road, Ealing, 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 **Company Presentation** Presentation by the MAH regarding the status of CAPAs from the last inspection (critical and major findings) and a summary of any additional key changes to the pharmacovigilance system. In particular, provide a summary in relation to the changes of service providers since the last inspection and the transfer of data. *(max. 45 minutes)*	[redacted]	Interviewee(s): All Welcome
Document review	-	Inspectors only
LUNCH	-	-
Control and maintenance of reference safety information ~~**Migration of pharmacovigilance data to a single global safety database/handling of pharmacovigilance data from multiple sources**~~	[redacted]	Interviewee(s): [redacted]

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MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	09 May 2017
LOCATION	APCER offices, C.P. House, 97-107 Uxbridge Road, Ealing, London W5 5TL	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Migration of pharmacovigilance data to a single global safety database/handling of pharmacovigilance data from multiple sources **~~Signal management~~**	[redacted]	[redacted]
Document review	-	Inspectors only
LUNCH	-	-
Signal management ~~Control and maintenance of reference safety information~~	[redacted]	[redacted]

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MHRA INSPECTION NUMBER	TBC	**DAY**	5
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	10 May 2017
LOCATION	APCER offices, C.P. House, 97-107 Uxbridge Road, Ealing, London W5 5TL	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Case processing	[redacted]	[redacted]
Document review	-	Inspectors only
LUNCH	-	-
Preparation and maintenance of Periodic Safety Update Reports	[redacted]	[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	6
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	10 May 2017
LOCATION	APCER offices, C.P. House, 97-107 Uxbridge Road, Ealing, London W5 5TL	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Quality Management System and Supervision and Oversight of the PV System • Audit programme • Management of audit findings and deviations • CAPA management • Maintenance and update of the PSMF • QPPV/MAH supervision and oversight	[redacted]	Interviewee(s): [redacted]
LUNCH	-	-
Document review		Inspectors only

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MHRA INSPECTION NUMBER	TBC	**DAY**	7
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Ltd.	**DATE**	10 May 2017
LOCATION	APCER offices, C.P. House, 97-107 Uxbridge Road, Ealing, London W5 5TL	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Roles and responsibilities of the QPPV/oversight of the PV system by the MAH	[redacted]	Interviewee(s): [redacted]
Document review		Inspectors only
LUNCH		-
Document review		Inspectors Only
Closing meeting		All welcome

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APPENDIX III EXAMPLES OF EVENTS REFERENCED IN FINDING MA.1 a) i

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Examples of events classified as non-serious in the [redacted] PSUR [redacted] which should potentially be classified as serious.

[redacted]	Suicide attempt
[redacted]	Suicide attempt
[redacted]	Acute psychosis
[redacted]	Neonatal respiratory distress syndrome
[redacted]	Cleft lip and palate
[redacted]	Heart disease congenital
[redacted]	Rhabdomyolysis
[redacted]	Suicide attempt
[redacted]	Anaphylactic shock
[redacted]	Acute myocardial infarction
[redacted]	Sepsis
[redacted]	Coma
[redacted]	Cardiac arrest