PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Cipla (EU) Limited

MHRA Inspection Number: GPvP 36390/1480807-0001

Medicines and Healthcare Products Regulatory Agency
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SECTION A: INSPECTION REPORT SUMMARY

Inspection Type:	Statutory Systems Inspection The UK is the Supervisory Authority for pharmacovigilance inspections in the EU. This inspection was conducted on behalf of the EU.
Name and address(es) of site(s) inspected:	Cipla (EU) Limited c/o APCER Pharma (Europe) Limited, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL NB: The inspection was performed at the office of the pharmacovigilance service provider.
Main site contact:	[redacted] c/o APCER Pharma (Europe) Limited, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL E-mail: [redacted] Telephone: [redacted]
Date(s) of Inspection:	24th – 26th June 2014
Lead Inspector:	[redacted]
Accompanying Inspector:	
Previous Inspection Date:	N/A – This was the MAH's first GPvP inspection
Purpose of Inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the general systems review, PSURs were examined for [redacted] centrally authorised product*), [redacted] and [redacted]
Name and location of EU/EEA qualified person for pharmacovigilance:	[redacted] APCER Pharma (Europe) Limited, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL E-mail: [redacted] Telephone: [redacted]
Global PV Database (in use at the time of the inspection):	ARISg (commercially available) version 5.1.2.3 ARGUS (commercially available)
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)

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Inspection Finding Summary:	1 Critical finding 3 Major findings
Date of first issue of report to MAH:	17th October 2014
Deadline for submission of responses by MAH:	21st November 2014
Date(s) of receipt of responses from MAH:	21st November 2014
Date of final version of report:	2nd June 2015
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background Information

Cipla (EU) Limited was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The inspection was also part of the EU plan for routine pharmacovigilance inspections of MAHs with centrally authorised products. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Regulation (EU) 1235/2010 amending Regulation 726/2004/EC, Directive 2010/84/EU amending Directive 2001/83/EC, 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, headquartered in X 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 and Cipla NV. Cipla Limited is focused on the manufacture and distribution of generic medicines At the time of the inspection, in excess of 100 authorisations were held by Cipla subsidiaries in the EU, authorised via national, mutual recognition and decentralised procedures. However, at the time of the inspection only a limited number of products had been launched onto the European market including seven products in the UK. Cipla Limited also hold authorisations outside of the EU in territories such as the US, Asia Pacific and Africa.

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Prior to the inspection, Cipla (EU) Limited held one central authorisation for [redacted] triggering inclusion of the MAH in the EU plan for routine pharmacovigilance inspections. However, the MAH declared during the opening meeting that a withdrawal notification for this product had been submitted to the EMA in May. The cancellation was confirmed by the European Commission on 8th July 2014.

EU pharmacovigilance activities, 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 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 included a review of both local and global pharmacovigilance systems, and was performed at APCER Pharma (EU) Limited's offices in Ealing, United Kingdom. Personnel from Cipla attended the APCER Pharma (EU) Limited office in order to participate in the inspection. Further personnel from Cipla located in India participated in the inspection via teleconference.

The inspection was performed using interviews and document and computer system reviews (including searches of the pharmacovigilance database/spreadsheets, medical

information and product quality databases). The inspection included a review of the roles and responsibilities of the EEA Qualified Person responsible for pharmacovigilance. 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 Pharmacovigilance System Master File (PSMF) document to assist with inspection planning and preparation. Line listings of reported adverse events, UK medical information enquiries and global product quality complaints, in addition to specific PSURs, 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).

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

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As the inspection was also part of the EU plan for routine pharmacovigilance inspections of MAHs with centrally authorised products, documentation including the PSUR for the centrally authorised product, [redacted] was requested. However, it was disclosed during the opening meeting that the marketing authorisation withdrawal notification had been submitted on 6th May 2014. Therefore, documentation reviewed during the inspection focussed on other products.

A closing meeting was held to review the inspection findings, at APCER Pharma (EU) Limited, Ealing, on 26th June 2014. 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.

Post-inspection documentation was received on 29th July 2014.

SECTION C: INSPECTION FINDINGS

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

Not applicable as this was the first MHRA pharmacovigilance inspection of the company.

C.2 Definitions of inspection finding gradings

Critical: 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: 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.

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

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: http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodPharmacovigilancePractice/Theinspectionprocess/index.htm

C.4 Inspection Findings

Critical Findings

C.4.1. Failure to establish a global pharmacovigilance system

Requirements:

Regulation 726/2004EC as amended, Article 21

Directive 2001/83 EC as amended, Articles 104 and 107

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

Commission Implementing Regulation (EU) No. 520/2012.

GVP Module I – Pharmacovigilance systems and their quality systems.

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

GVP Module VII – Periodic Safety Update Report.

At the time of the inspection the Cipla parent organisation, Cipla Limited, had EU marketing authorisations registered under the subsidiaries Cipla (UK) Limited, Cipla (EU) Limited and Cipla Europe NV. At the time of the inspection 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.
- S43 A second system was in place in the EU incorporating all products authorised to Cipla (UK) Limited and outsourced to S&D Pharma CZ to perform pharmacovigilance activities behalf of the MAH and hosted in the Czech Republic.
- A third system was maintained by the Cipla headquarter organisation, based in India, which collected and reviewed data originating from all non-EU territories. AE data was collected and entered into an ARGUS database.

At the time of the inspection the MAH had failed to establish a global pharmacovigilance system, as demonstrated by the following deficiencies:

Finding C.4.1 a

At the time of the inspection global safety data associated with Cipla products were not accessible at a single point within the EU.

Directive 2001/83 EC as amended article 107 (1) states:

"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."

i. There was no mechanism to access the safety information present in the ARGUS database within the EU. At the time of the inspection Cipla were maintaining multiple safety databases based on the region from which an AE report originated from. All cases reported from within the EU were entered into an ARISg database, maintained and accessed by the service provider APCER. AE reports originating from the rest of the world were received directly by the Cipla Drug Safety Division (DSD) based in India and entered into an ARGUS database.

ii. It was determined during the inspection that there were 16 active substances that were authorised to both Cipla (UK) Limited and Cipla (EU) Limited (a full listing of the shared active substances is included in Appendix II). At the time of the inspection, there was no mechanism for the exchange of safety data between the Cipla subsidiaries or a mechanism to allow access to the AE reports stored in the safety database maintained by S&D Pharma. As a result not all safety data was accessible at a single point in the EU.

Root Cause Analysis

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[redacted]

S43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

S43

Deliverable(s)	Due Date(s)

Preventative Action(s)

S43

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

Finding C.4.1 b

Failures in expedited reporting

Reports originating from third countries and processed by Cipla India (and entered into the ARGUS database) were not considered for expedited reporting to EU Competent Authorities. During the inspection the following spontaneous, serious cases were identified in the ARGUS database which had not been expedited:

Reference number	Country of origin	Suspect Drug	Adverse event(s)
[redacted]	United States	[redacted]	Neutrophil count decreased
[redacted]	India	[redacted]	Hepatic failure, dyspnoea

It is acknowledged that the APCER performed a global literature search which was designed to identify any global ICSRs for expedited reporting. At the time of the inspection the MAH had received very little unique data (as products had only recently been launched onto the market in many territories) and the majority of non-EU data was derived from the scientific literature.

Post-inspection request: As part of the inspection responses the MAH should review the data recorded in the ARGUS database to determine whether any cases require expedited reporting to EU Competent Authorities and provide the result within the response.

Root Cause Analysis

[redacted]

Further Assessment

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

S43

[redacted]

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

Finding C.4.1.c

Failures to include global safety data in ongoing monitoring activities

i. There was no mechanism to retrieve data from the ARGUS database for inclusion in signal detection activities performed by APCER. For example in April 2014 a signal detection meeting was held and potential signals discussed:

- [redacted] and myelodysplastic syndrome: 2 cases were identified in the ARISg database [redacted]. However an additional two cases were identified in the ARGUS database during the inspection [redacted] and [redacted].
- [redacted] and cerebral infarction: One case was identified in the ARISg database [redacted]. However an additional case was identified in the ARGUS database during the inspection [redacted]

ii. There was no mechanism to retrieve AE reports from the S&D Pharma database for inclusion in signal detection activities. Therefore the signal detection activities were not performed on a cumulative global dataset.

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]

S43

[redacted]

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

Finding C.4.1 d
i. There was no mechanism to retrieve data from the ARGUS database for inclusion in PSURs submitted to EU Competent Authorities. ii. Additionally, there was no mechanism to retrieve AE reports received by S&D Pharma database for inclusion in PSURs. It is acknowledged that AE reports collected via the S&D Pharma pharmacovigilance system would be included in separate PSURs produced by S&D Pharma. However, neither the APCER nor S&D Pharma CZ PSURs would be representative of the global AE dataset associated with the shared products.
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]	

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Finding C.4.1 e

At the time of the inspection both the Cipla Drug Safety Division (Cipla DSD), based in India, and APCER, based in the UK, were performing pharmacovigilance activities for products authorised in the EU. However, there was no oversight by the EU-QPPV of the outcomes of the pharmacovigilance activities performed by Cipla DSD. For example:

i. Cipla DSD was producing PSURs based on data held within the ARGUS database for submission to non-EU territories. There was no mechanism to share the PSUR recommendations and outcome with the EU-QPPV. For example Cipla DSD produced a PSUR fo[redacted] for submission to the Egyptian authorities with a DLP of 20-Jun-2012. A separate PSUR was produced by APCER for submission to the MHRA with a DLP 21-Sep-2011 to 01-Jan-2013. The conclusions made in the Cipla DSD PSUR were not shared with the APCER team responsible for producing PSURs for submission to EU Competent Authorities.

ii. Cipla DSD was performing signal detection disproportionality analyses for products authorised outside of the EU using data entered into the ARGUS database. There was significant overlap with the product portfolio authorised in the EU. At the time of the inspection there was no mechanism for the EU-QPPV to be made aware of the outcome of these activities. For example, a Signal Management Report (approved 31-Mar-2014) covering the period 10-Jul-2011 to 31-Dec-2013 was produced, identifying 234 signals of disproportionate reporting. Review of these potential signals determined that no further action was required. The outcome of this review was not shared with the EU-QPPV.

iii. Cipla DSD was performing a global literature search using a different search strategy to the search utilised by APCER in the EU. The Cipla search was a broad search based on the active substance name, whilst the APCER literature search was more focussed. There was no mechanism for any articles identified by the Cipla search which may not had been identified by APCER to be exchanged.

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]	

S43

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

Finding C.4.1 f

At the time of the inspection there was no global oversight of the commercial agreements in which the MAH were engaged. As a result during the inspection the MAH were unable to confirm whether appropriate pharmacovigilance relevant language was included within the existing commercial agreement of whether a separate Safety Data Exchange Agreement was in place to support the transfer of any adverse event (AE reports) received by the partner organisation in relation to a Cipla product. Consequently the MAH were unable to meet their obligation to ensure that safety data was appropriately collected from all sources. Directive 2001/83 EC as amended, Article 107 (1) states: *"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*

Post-inspection the MAH were asked to determine what organisations they had entered into contractual agreements with and the status of safety data exchange and the following noted:

i. The MAH identified 110 distribution partners (distribution partner defined as Cipla maintaining the marketing authorisation in that territory, partner acting as the local distributor), 107 of which did not have SDEAs in place. Furthermore, no AE reports had been received from any of the distribution partners, despite in some instances there being high volumes of sales. For example:

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Partner	Territory	Date commercial agreement signed	Sales volume (pack sales)
[redacted]	Africa	15-Apr-2013	386,335
[redacted]	Iran	N/A no formal agreement signed. Commercial agreement currently under discussion	9,549,454
[redacted]	Kenya	01-Jun-2009	881,744

ii. A further 77 licensing partners (licensing partner defined as Cipla holding a marketing authorisation in Europe, and the partner holding the MA in other territories) were identified; however, no assessment had been made to determine whether a SDEAs would be required. Furthermore, no AE reports had been received from any of the licensing partners, despite in some instances there being high volumes of sales. For example:

Partner	Territory	Date commercial agreement signed	Sales volume
[redacted]	Thailand	11-Feb-2002	64,225

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[redacted]	Australia	15-Feb-2012	47,188
[redacted]	Australia	04-Apr-2009	58,896

Post-inspection request: As part of the responses, the MAH should propose how they will approach ensuring that appropriate safety data exchange agreements are put in place with existing partners. The MAH should also perform a retrospective reconciliation exercise with all partners to ensure that they are in receipt of all relevant safety information.

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]	

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Major Findings

C.4.2 Control and maintenance of Reference Safety Information

Requirements:

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

Directive 2001/83/EC as amended. Paragraph 40, Article 23 (3)CPMP/ICH/135/95, (E6). Section 7.1.

Volume 2 Eudralex, Pharmaceutical Legislation: Notice to Applicants. Volume 2C – Regulatory Guidelines: Guideline on Summary of Product Characteristics. Revision 2 September 2009. Section 10 Date of Revision of the Text.

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.

At the time of the inspection the majority of the product portfolio had not been launched onto the UK market. A limited number of products had been launched shortly prior to the start of the inspection (earliest launch in the UK was February 2014). At the time of the inspection the MAH tracked all safety variations using an excel-based tracking system an extract of which was provided during the inspection. Review of the tracking system identified safety variations that had not been submitted as the product was not marketed at the time that the change had been identified. It was described during interview that the variation would be submitted at the next regulatory opportunity or prior to product launch. The following deficiencies were noted:

Finding C.4.2 a

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At the time of the inspection multiple failures to include the most up-to-date PIL in product packs were identified:

i. An update to the [redacted] 5mg tablets SPC was identified in the PSUR DLP 28-Aug-2012. The update included additions to sections 4.1. 4.2, 4.3, 4.4, 4.5, 4.6, 4.7 and 4.8. A variation was not submitted at the time as the product was not marketed in any EU territory. Following a decision by the organisation to launch the product a safety variation was submitted to the MHRA on 03-Oct-2013 and approved on the 04-Jun-2014. However the first batch of product released to the UK distributor [redacted] was on 01-May-2014, prior to the variation approval. As a result the previous PIL dated November 2013 was included in these product packs. A description of the omitted information is provided in Appendix IV.

ii. An update to the [redacted] SPC was requested by the Reference Member State (and other Concerned Member States) during a Repeat Use procedure (RUP), following a comparison with the reference products product information. As these changes could not be applied during the RUP the MAH were requested to submit a variation following closure of the procedure. The RUP was approved on the 29-Jan-2014, and a variation submitted by the MAH on 05-Mar-2014. However, the MAH launched the product onto the UK market on 05-Feb-2014, without the changes requested during the RUP. The changes requested following

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the RUP are summarised in Appendix V.
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]	

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Finding C.4.2 b
During the inspection, the steps taken pre-launch were described. However, there was no formal documented procedure that specifically described the requirement to ensure that the SPC/PILs were fully up-to-date with all safety information prior to launch onto the market. There was also no mechanism to ensure that all variations had been approved and implemented prior to going ahead with the launch, as demonstrated by the examples above.
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]	

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Finding C.4.2 c	
Following a variation request from a Competent Authority there was no process in place to review product information in other territories to determine whether the requested updates would be appropriate for inclusion. A post-inspection document request determined that requests had been received from non-EU authorities to update the product information. As part of the inspection responses the MAH are asked to review the requested changes and if this information is not already represented in the EU product information (SPCs/PILs) confirm whether these updates need to be applied. A list of the requests received is included in Appendix VI.	
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]	

Finding C.4.2 d

During the inspection, multiple errors in the determination of the date of the revision of text, presented in Section 10 of the SPC were identified.

Eudralex 2C A guideline on Summary of Product Characteristics states:

"10 DATE OF REVISION OF THE TEXT

Leave blank in case of a first Marketing Authorisation.

For medicinal products for which the European Commission is the Competent Authority: date of approval of latest variation or transfer, e.g. the latest Commission Decision amending the SmPC, implementation date of the Urgent Safety Restriction or date of (EMEA) notification amending the annexes to the Marketing Authorisation.

For products for which Member States are the Competent Authorities: date of approval of latest variation or implementation date of the Urgent Safety Restriction resulting in a revision of the SmPC."

There were multiple examples where the date of the revision of the text did not reflect the date that the last variation was approved for example:

Product	Last variation approval date	Date of the revision of text
[redacted]	04-Jun-2014	April-2014
[redacted]	22-Nov-2013	Aug-2013
[redacted]	10-Mar-2014	Feb-2014

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

C.4.3. Signal Management

Requirements:

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

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

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 C.4.3 a

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Signals that were listed on a tracking spreadsheet were not evaluated in a timely and appropriate manner. Multiple examples were identified where evaluations had been delayed by several years and where a full cumulative review of all sources of safety data had not been undertaken. For example:

i. [redacted]and Acute/Chronic Renal Failure

This drug-event pair was detected in January 2012 and 22 cases had been identified from literature and Health Authority reports. The status of the signal review was stated on the spreadsheet as 'N/A' and the date of review finalisation stated as 'to be prepared'.

ii. [redacted]and Acute/Chronic Renal Failure

This drug-event pair was detected in April 2013 and 15 cases had been identified from literature. The status of the signal review was stated on the spreadsheet as 'N/A' and the date of review finalisation stated as 'to be prepared'.

iii. [redacted]and Neuropathy

This drug-event pair was detected in October 2012 and 13 cases had been identified from literature and Health Authority reports. The status of the signal review was stated on the spreadsheet as 'N/A' and the date of review finalisation stated as 'to be prepared'.

iv. [redacted]and Torsade de pointes

This drug-event pair was detected in January 2012 and 9 cases had been identified from literature and Health Authority reports. The status of the signal review was stated on the spreadsheet as 'N/A' and the date of review finalisation stated as 'N/A'.

Post-inspection actions: The MAH should conduct and document signal evaluations for all unlabelled signals where no full review has previously been conducted, including for closed signals, i.e. to determine whether appropriate evaluations were undertaken prior to signal closure. This must include an evaluation of all case information and information available in published literature.

This has been reported as a Major finding rather than a Critical, due to the non-marketed status of the majority of the portfolio in the EU, there was no impact with regards to the

information available to healthcare professionals and patients regarding these products. Additionally, the failure to include worldwide ICSRs in signal detection activities has been reported separately as part of the critical finding C.4.1 c.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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Deliverable(s)	Due Date(s)

Preventative Action(s)

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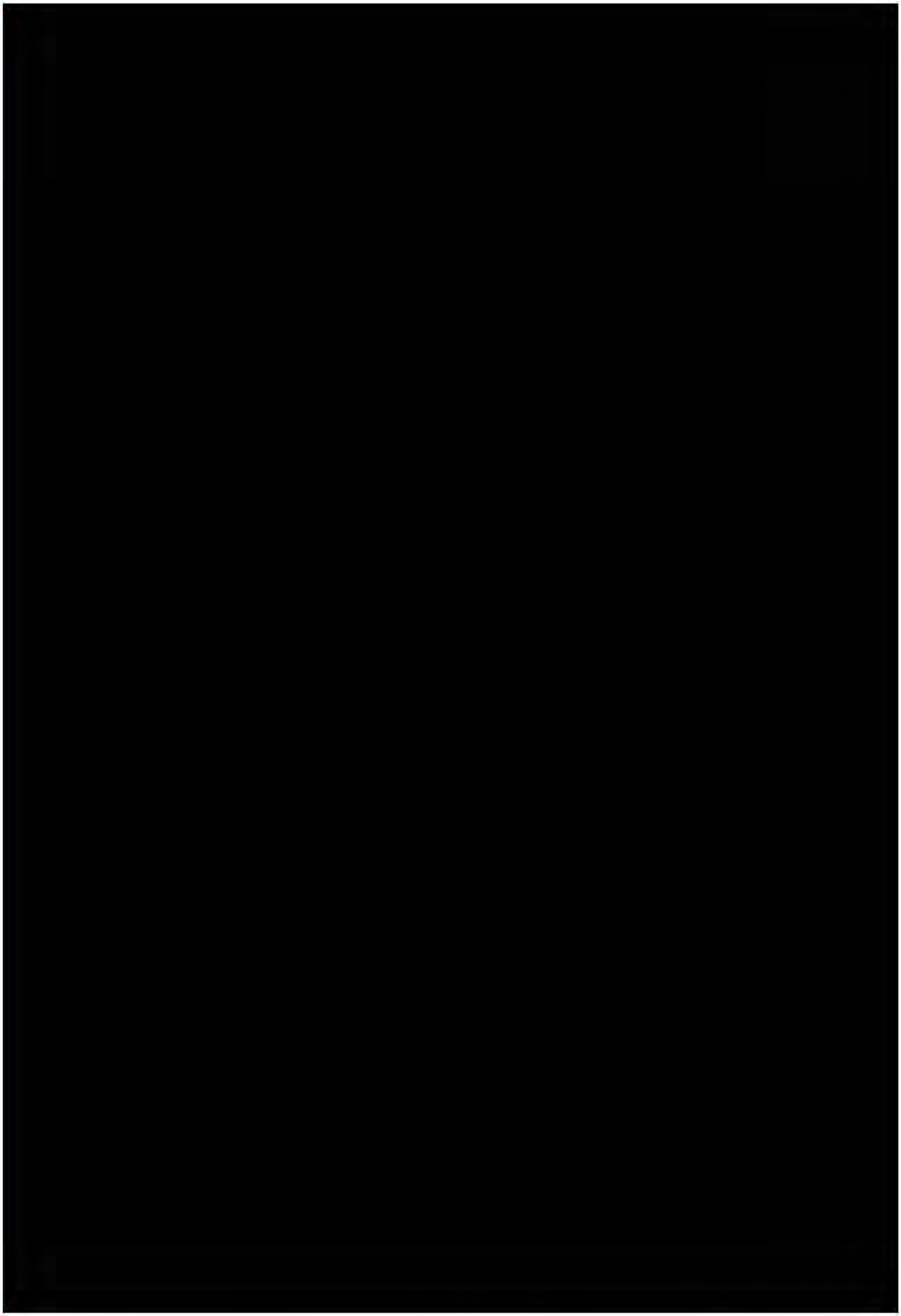

S43

[redacted]

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

Finding C.4.3 b
The signal detection SOP [redacted] Signal Detection and Safety Monitoring (effective [redacted] was deficient. It was noted that two excel listings were used to track potential and on-going safety signals. This included one which was described as "ADRs to monitor" and one which was described as "ongoing signals". The use of these trackers was not defined in the signal SOP and there were no documented criteria for when an ADR should be considered "for monitoring" and when it would be considered an ongoing signal.
Root Cause Analysis
[redacted]

S43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

S43

[redacted]

Finding C.4.3 c
At the time of the inspection, there was no process for routine cumulative review to detect new safety signals. Signal detection was conducted on a monthly basis for all products and based solely upon individual case review of adverse reactions received in the preceding one month period. Only when an adverse reaction reported in the monthly line-listing was considered "biologically plausible", did the EU-QPPV evaluate the data in light of the full cumulative experience for that product.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

S43

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

Preventative Action(s)
[redacted]

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

Finding C.4.3 d
Information reported in the scientific literature was not formally considered in the signal detection process unless it contained valid case reports. Relevant safety publications which did not contain individual case data or those publications with invalid adverse reactions were not formally considered in signal detection.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)

S43

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding C.4.3 e

The signal tracker was incomplete and did not comply with the format as outlined in GVP Module IX. It simply contained a list of drug event pairs under monitoring. It did not record any of the validation, prioritisation, assessment, timelines, decisions, actions, plans, or reporting steps.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)

S43

[redacted]

Preventative Action(s)
[redacted]

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

Finding C.4.3 f
There was no documented process or frequency for review of the EMA web portal or the PRAC meeting minutes. It was noted that, at the time of the inspection, a procedure that covers this activity was in draft and due for imminent release.

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)

S43

[redacted]

C.4.4. Quality Management System

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 184.

Commission Implementing Regulation (EU) No. 520/2012, Chapter 2.

GVP Module I – Pharmacovigilance systems and their quality systems.

GVP Module II – Pharmacovigilance System Master File.

GVP Module IV – Pharmacovigilance audits

At the time of the inspection, there were two audit programmes; one managed by Cipla that included audits of their Drug Safety Division (DSD), their worldwide affiliates and of APCER UK and APCER India; and one managed by APCER that was included internal audits.

The following findings were noted in relation to the quality management system which is used to support the MAH's pharmacovigilance system:

Finding C.4.4 a

Quality Assurance Auditing

i. There was no strategic level audit plan which outlined the companies audit strategy over a 2-5 year period (as outlined in GVP Module IV.B.2.1: "*The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years.*").

ii. There was no documented risk-based audit strategy to determine the topics and frequency of MAH/APCER audits, as required by GVP Module IV.B.2, which states: "*Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation…*"). Such a strategy should define the factors to be considered in th e risk-based approach.

Root Cause Analysis

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[redacted]

Further Assessment

[redacted]

S43

[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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Finding C.4.4 b
Quality Assurance Auditing The Cipla or APCER audit programme did not include audits of Cipla licensing and distribution partners. In addition, there were no other mechanisms to determine the compliance of partners with regards to collection and transfer of adverse event reports to the MAH.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

S44

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

Finding C.4.4 c
Quality Assurance Auditing There was no documented evidence that the Cipla personnel who conducted the APCER UK and APCER India pharmacovigilance audits, had received any audit training. GVP Module I states: "*Adequate training should also be considered by the organisation for those staff members…whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to…audits.*" It is noted, however, that all three auditors had extensive experience in pharmacovigilance.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

S43

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding C.4.4 d

Procedural Documentation

Cipla SOP [redacted] on *Document Retention and Destruction* contained a retention period of ten (10) years from the date of archiving.

GVP Module I states: "*…the marketing authorisation holder shall put in place the following additional specific quality system processes for ensuring: …the retention of pharmacovigilance data and documents relating to individual authorised medicinal products as long as the marketing authorisation exists and for at least further 10 years after the marketing authorisation has ceased to exist [IR Art 12(2)];*"

Root Cause Analysis

[redacted]

S43

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

APPENDIX I: REFERENCE TEXTS

- Directive 2001/83/EC, as amended by Council Directives 2004/27/EC, 2010/84/EU and Commission Directive 2003/63/EC.
- EU Regulation 726/2004 (Title II, Chapter 3), as amended by EU Regulation 1235/2010.
- Commission Implementing Regulation (EU) No 520/2012.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP) Modules.
- Volume 9A of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use, September 2008.
- Commission Regulation EC 540/95.
- Regulation (EC) No 1901/2006 and Regulation (EC) No 1902/2006.
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance.
- 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".
- CPMP/ICH/288/95: E2C (R1) "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs".
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- 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	GPvP 36390/1480807-0001	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Limited	**DATE**	24th June 2014
LOCATION	APCER Pharma (Europe) Ltd, 9th Floor, CP House, 97-107 Uxbridge Road, London W5 5TL	**START TIME**	09:30

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting • review of scope of inspection and inspection plan • overview of the company and pharmacovigilance system *(presentation by MAH to be no longer than 20 minutes)*	[redacted]	All welcome Cipla team & APCER UK team [redacted]
Receipt and handling of medical information enquiries and product quality complaints		Interviewee(s): Cipla: [redacted] APCER UK: [redacted] APCER INDIA: [redacted] Singla APCER USA: [redacted]
LUNCH	-	-

S40

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Review of processing, follow-up and submission of adverse reaction reports • management of regulatory authority cases • management of spontaneous cases, including coding, evaluation, follow-up and submission • literature searching and review	[redacted]	Interviewee(s): Cipla: [redacted] APCER UK: [redacted] APCER INDIA: [redacted]
Document Review	-	Inspectors only

[redacted]

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]

Cipla (EU) Limited: [redacted]

APCER Pharma Europe Limited: [redacted]

APCER Pharma India Limited : [redacted]

APCER Pharma Solutions Inc. (USA): [redacted]

MHRA INSPECTION NUMBER	GPvP 36390/1480807-0001	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Limited	**DATE**	25th June 2014
LOCATION	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**
PSUR production and co-ordination	[redacted]	Interviewee(s): Cipla: [redacted] APCER UK: [redacted] APCER INDIA: [redacted]
Ongoing safety monitoring/signal detection activities and RMP maintenance	[redacted]	Interviewee(s): Cipla: [redacted] APCER UK: [redacted]
LUNCH	-	-

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Maintenance of reference safety information, including core safety information, SPCs, PILs	[redacted]	Interviewee(s): Cipla: [redacted] APCER UK: [redacted]
Document Review	-	Inspectors only

MHRA INSPECTION NUMBER	GPvP 36390/1480807-0001	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Cipla (EU) Limited	**DATE**	26th June 2014
LOCATION	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 • pharmacovigilance policies/procedures • pharmacovigilance training • auditing of pharmacovigilance activities conducted by CIPLA and APCER • maintenance of the PSMF	[redacted]	Interviewee(s): Cipla: [redacted] APCER UK: [redacted]
LUNCH	-	-
Roles and responsibilities of EU/EEA Qualified Person	[redacted]	Interviewee(s): Cipla: [redacted] APCER UK: [redacted]
Document review	-	Inspectors only
Inspectors meeting	-	Inspectors only
Closing Meeting	[redacted]	[redacted] welcome

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APPENDIX III: SHARED ACTIVE SUBSTANCES

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Active substance	EU Territory(ies)	
	Cipla (UK) Limited	Cipla (EU) Limited
[redacted]	Romania	UK
[redacted]	Romania	UK
[redacted]	Romania	UK
[redacted]	Romania	Ireland, (under registration)
[redacted]	Czech Republic, Slovak Republic	UK
[redacted]	Latvia	UK
[redacted]	Bulgaria	UK
[redacted]	Czech Republic	UK (authorised) Sweden, Germany, Spain, Portugal, Italy, France, Denmark, Finland, Poland, Norway, Hungary, Croatia, Slovak Republic (under registration)
[redacted]	Czech Republic, Latvia	UK
[redacted]	Latvia	UK
[redacted]	Romania, Latvia	UK
[redacted]	Romania	UK
[redacted]	Romania	UK
[redacted]	Latvia	UK
[redacted]	Romania, Czech Republic	UK
[redacted]	Latvia	Under registration

APPENDIX IV: PIL COMPARISON

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PIL Section	Information present in PIL approved on 04-Jun-2014 but omitted in the PIL released into product packs
Section 2: Before you take [redacted]	Take special care with [redacted] • If you have a large amount of residual urine or severly reduced urinary flow. • If you notice any changes in your breast such as lumps, pain, gynaecomastia (breast enlargement) or nipple discharge.
Section 4: Possible side effects	Frequency of these allergic reactions are unknown: If you have an allergic reaction stop taking and see your doctor straight away. The signs may include: • Skin rashes, itching or lumps under your skin (hives) • Swelling of your lips, tongue, throat and face. Not known (cannot be determined from available data): • Testicular pain, feeling your heartbeat, increased liver enzymes. • Less desire to have sex even after discontinuing treatment • Depression • Itching • Hives • Sexual dysfunction which may continue after discontinuation of treatment. • Male infertility and/or poor quality semen (normalisation or improvement of seminal quality has been reported after discontinuation of [redacted]

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APPENDIX V: CHANGES REQUESTED TO [redacted] SPC FOLLOWING REPEAT USE PROCEDURE

SPC Section	Addition
Section 4.1	Update: "indicated for use in adults and children 12 6 years of age and older…"
Section 4.4	Growth retardation has been reported in children receiving nasal [redacted] at the licensed dose. [redacted] contains [redacted] which is an irritant that may cause nasal irritation. If used for a longer period, the preservative [redacted] may cause nasal mucosa swelling. In the case of such a reaction (persistently congested nose) then preservative-free medicinal products for nasal use should be used if possible; however if such preservative-free medicinal products are not available another pharmaceutical form should be used (see section 5.3).
Section 4.8	As with other intranasal [redacted] rare cases of nasal septum perforation have been reported. Rare cases of glaucoma, increased intraocular pressure and/or cataracts have been reported with the use of intranasal [redacted]

APPENDIX VI: COMPETENT AUTHORITY VARIATION REQUESTS

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Country	Regulatory authority	Product	Date of issue of letter	Nature of change
Colombia	INVIMA	[redacted]	08/08/2012	Suicidal behaviours with [redacted]
Colombia	INVIMA	[redacted]	08/08/2012	Suicidal behaviours with [redacted]
Colombia	INVIMA	[redacted]	08/08/2012	Suicidal behaviours with [redacted]
Colombia	INVIMA	[redacted]	08/08/2012	Suicidal behaviours with [redacted]
Oman	Sultanate of Oman, Ministry of Health	[redacted]	25/08/2013	Addition of fatal arrhythmias
Ghana	Food & Drugs Authority	[redacted] containing products	25/11/2013	Restrictions and contraindications: • Analgesia in children and adolescents • Breastfeeding women • Symptoms of codeine toxicity
Ghana	Food & Drugs Authority	[redacted] containing products	29/11/2013	Rare but serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis
Republic of Sudan	National Medicines & Poisons Board	[redacted]	14/08/2013	Warnings regarding neurologic and psychiatric side effects
United Arab Emirates	Ministry of Health	[redacted]	11/11/2013	Update side effects to be in line with the BNF