Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Dr Reddy's

MHRA Inspection Number: Insp GPvP 8553/18014-0021

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EU	European Union
EUCSI	European Union Core Safety Information
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SmPC	EU Summary of Product Characteristics

SOP	Standard Operating Procedure
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Dr Reddy's, [redacted]
Site(s) of inspection:	Dr Reddy's Laboratories (EU) Ltd, 410 Cambridge Science Park, Milton Road Cambridge, CB4 0PE
Main site contact:	[redacted] Dr Reddy's Laboratories SA Elisabethenanlage 11 CH-405 Basel, Switzerland [redacted]
Date(s) of inspection:	16 October 2019 (remote inspection) 21-23 October 2019 (onsite inspection)
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	9-10 November 2010 16-18 March 2010 9-11 August 2006 26-28 July 2005
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Name and location of EU QPPV:	[redacted] betapharm Arzneimittel GmbH Kobelweg 95, 86156 Augsburg Germany [redacted]
Global PV database (in use at the time of the inspection):	LifeSphere Safety MultiVigilance (ARISg) [redacted]
Key service provider(s):	ICSR management and PSUR production were outsourced to iSafety. Medical information services were provided by ProPharma.
Inspection finding summary:	01 Critical finding 06 Major findings 02 Minor findings
Date of first issue of report to MAH:	v1 first issued 28 November 2019, v2 issued 19 February 2020
Deadline for submission of responses by MAH:	06 January 2020
Date(s) of receipt of responses from MAH:	06 January 2020, 03 February 2020, 04 March 2020
Date of final version of report:	06 March 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Dr Reddy's was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at Appendix I.

Dr Reddy's is an international pharmaceutical company with a global generics business, selling branded and unbranded products in markets around the world, including significant activity in North America, India and Europe. In the UK, Dr Reddy's has 200 national licences in the UK under the name Dr Reddy's Laboratories (UK) Ltd. ICSR management and PSUR production has been outsourced to third party service provider iSafety. The QPPV is based at Dr Reddy's in Germany.

B.2 Scope of the inspection

The inspection included a review of the local global pharmacovigilance system and was performed at Dr Reddy's offices in Cambridge Science Park. Personnel from Dr Reddy's and iSafety attended the Cambridge site in order to participate in the inspection. Personnel from Dr Reddy's also participated remotely through teleconference.

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

Topics in relation to signal management were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

B.3 Documents submitted prior to the inspection

The company submitted a PSMF ([redacted] dated 23 August 2019) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the inspection plan. Minor amendments to the Inspection Plan that occurred during the inspection are highlighted using italic text in Appendix II. A day of inspection was conducted remotely on 16 October 2019, prior to the inspection days onsite.

A closing meeting was held to review the inspection findings at Dr Reddy's, Cambridge, on 23 October 2019. A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

Following the inspection, a post inspection letter was issued to the company on 24 October 2019, to outline immediate actions required in relation to major findings MA1.a, MA.1b and MA2a. An additional 1.5 days of remote inspection were required to complete the review of data from the inspection and the information submitted in response to this letter.

SECTION C: INSPECTION FINDINGS

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

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

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- Outsourced global pharmacovigilance activities of ICSR management and medical writing (including aggregate report preparation) were transferred from Parexel to iSafety in November 2018.
- The QPPV changed from [redacted] in July 2019.
- During 2019, scheduling and conducting pharmacovigilance audits was being transferred from the EU pharmacovigilance department to the Dr Reddy's QA department.
- The company was in the process of implementing a new global regulatory information management system (RIMS) linked to the existing SAP enterprise resource planning software, due to go live in 2020.

C.2 Definitions of inspection finding gradings

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

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

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

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

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

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

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

CR.1 Implementation of approved updates to product safety information

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During the inspection, evidence of non-compliance with the requirements to keep product information up to date was identified, specifically in the release of nine batches of [redacted] that were certified containing out of date patient information leaflets.

A further investigation, initiated by Dr Reddy's during the inspection, identified that this was not an isolated example, and was caused by systematic failures in the company processes to ensure that patient information leaflets (PILs) containing updated safety information were being introduced in released batches of product in a timely fashion and within regulatory expectations.

This finding was initially graded as major, however, in view of the outcomes from the full investigation, the delays in providing patients with up to date information on known product risks are considered to adversely affect the rights, safety or well-being of patients and poses a potential risk to public health. Consequently, the finding has been regraded to critical.

Finding CR.1

During the inspection, it was identified that four batches of [redacted] and five batches of [redacted] were released with out of date PILs missing updates to safety information. A Type [redacted] variation to harmonise the product information with the originator had been approved on 05 October 2018.

Updated safety information included warnings to section 2 of the PIL about possible interactions when taking 'mechanistic target of [redacted] inhibitors concomitantly with [redacted] Two batches (batch [redacted] were certified on 26 September 2019, nearly a year after variation approval, whilst the remaining eight batches (batch IDs: [redacted] were certified between 21 June 2019 and 27 June 2019, 8-9 months after variation approval. A further three batches (batch IDs: [redacted] had not been QP certified at the time of the inspection and contained an out of date version of the PIL.

Guidance published by the MHRA states that once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months:
https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets.

Immediate actions to be taken by the MAH were summarised in a Post Inspection Letter sent to Dr Reddy's on 24 October 2019 (refer to Appendix III) and the MAH committed to conduct an investigation into this non-compliance and to provide assurance of the compliance of batches on QP certification. The report with findings from this investigation are in Appendix III.

The investigation found that over the three year period reviewed by the MAH, 58 additional batches for seven substances were identified to have been certified out of compliance, containing outdated PILs beyond the maximum six months to implement updated leaflets.

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Details of all affected batches listed in the investigation report from the MAH as having been non-compliantly QP certified, were reviewed by the MHRA's Defective Medicines Reporting Centre (DMRC). A Class [redacted] drug alert was published on 29 January 2020 concerning 30 batches of [redacted] that were certified with out of date leaflets beyond the 6 months deadline, four of these almost 14 months beyond that deadline. The leaflets were missing important warnings following the addition to the SmPC of the warning:

[redacted]

For other affected batches yet to be QP certified, the MAH were advised to submit batch-specific variations to the MHRA, if rework of the batches was not planned.

Root Cause Analysis

[redacted]

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Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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[redacted]

Preventative Action(s)

[redacted]

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[redacted]

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

C.4.2 Major findings

MA.1 Maintenance of product safety information

Requirements:

Directive 2001/83/EC as amended,
Paragraph 40 *"The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information."*
Article 23(3) *"The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge"*

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

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

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

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

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Finding MA.1 a)

Variations to update the product information with significant safety information had not been submitted for two [redacted] products:

i) [redacted] The need for harmonisation of the [redacted] product information with the originator was identified following the annual signal detection review completed in February 2018. A change control request for this update was raised in April 2018, however the change request did not enter the change control system at Dr Reddy's and no variation was submitted. Safety related updates within this variation included the following:

- Section 4.2 - Addition of an instruction (bold print) that the patch must not be divided or cut into pieces.
- Section 4.4 - Addition of warnings about use in patients with acute alcohol intoxication and the need to titrate [redacted] dosage in patients concomitantly treated with [redacted] nhibitors.
- Section 4.8 - Addition of the following reactions: aggression, seizures,

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orthostatic hypotension, dermatitis contact, drug withdrawal syndrome neonatal (to note, a warning on this was already included in section 4.6).

The need for harmonisation was again identified in the signal detection review completed in January 2019 (dated March 2019), where it was stated that a change control request was raised in April 2018. As stated in section [redacted] of EU-SOP-PV-[redacted] SmPC 'Safety updates' (effective 01 November 2018), the default timeline for safety update submission was 120 days, if not otherwise specified. The signal detection review was signed by the QPPV 11 months after the change control request was raised, yet no further action was taken to identify why the variation had not been implemented in this time.

ii) [redacted] In February 2018 the CMDh published advice that harmonised texts should be included within EEA product information concerning warnings on the concomitant use of [redacted] Proposed text for SmPC sections 4.4 and 4.5 and PIL section 2 was published for both [redacted] licences. Although this advice was identified by the MAH, as documented in the [redacted] signal detection review for the period 01 February 2018-31 January 2019, a safety variation was not submitted to add this warning to the [redacted] product information. During the inspection, the MAH stated that the variation would not be submitted until the originator implemented the wording into their SmPC and PIL. Given that proposed wording was provided by CMDh, the rationale provided is not considered appropriate.

A further example of a delay to submit a safety variation was identified:

iii) The MAH was aware of the need to submit a safety variation to update the [redacted] product information with warnings about phototoxicity (SmPC section 4.4) and pseudoporphyria (SmPC section 4.8) in December 2018 (as documented in the [redacted] signal detection review). The Commission decision for the corresponding [redacted] variation of the originator [redacted] was issued on 25 June 2018. This variation was not submitted until 15 July 2019 by the MAH, over six months after the documented awareness in the signal detection review. This was incorrectly recorded as an on time submission in the tracker used to monitor submission of safety variations as date of decision as had been incorrectly recorded as 28 March 2019.

It is the expectation of the MHRA that variations to update the safety sections of SmPCs and PILs are submitted within a maximum of six months of the identification date, unless a shorter timeframe has been specified by a regulatory authority, to ensure compliance with the requirements in Directive 2001/83/EC as amended Article 23(3).

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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[redacted]

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

Finding MA.1 b)
Dr Reddy's published information on their marketed products through the UK electronic Medicines Compendium (eMC) website, however examples were identified where Dr Reddy's had failed to keep this information up to date. Out of the seven examples reviewed, there were delays of one to four months in updating the information for five products: i) Type [redacted] variation to add impulse control disorders to section 4.4 of the [redacted] SmPC (harmonisation activity). The variation was approved on 07 November 2018 and eMC was updated 22 March 2019. ii) Type [redacted] variation to add a warning to sections 4.4 and 4.8 of the [redacted] SmPC regarding autoimmune hepatitis (PRAC recommendation). The variation was submitted 05 November 2018 and eMC was updated 31 January 2019. iii) Type [redacted] variation to add interstitial lung disease to section 4.8 of the [redacted] SmPC (PRAC recommendation). The variation was submitted 27 November 2018 and eMC was updated 16 January 2019. iv) Type [redacted] variation to add a warning to section 4.4 of the [redacted] SmPC regarding aortic aneurysms (PRAC recommendation). The variation was submitted

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on 12 December 2018 and eMC was updated 10 January 2019.

v) Type [redacted] variation to add anxiety to section 4.8 of the [redacted] SmPC (PSUSA requirement), the variation was submitted on 07 August 2018 and eMC was updated on 17 October 2018.

To note, the dates provided above are of the published updates on the eMC website rather than when updates were uploaded to eMC, evidence of which was not available during the inspection. It is recognised that there may be a delay between upload of the updates and their publish on eMC website and update, although as confirmed in the interview session, this is unlikely to be more than one week. The above examples represent delays of a minimum of 29 days.

It is the expectation of the MHRA that product information published on the eMC website is updated within 10 working days of updating the information. For a type [redacted] 'do and tell' variation, this timeframe starts on the date that the variation was submitted, while for other variations, this timeframe would start on the date of variation approval. The timeline specified in the Dr Reddy's SOP is 10 calendar days (section 5.4.1 of UK [redacted] 'Maintenance of SmPCs and PILs on the electronic Medicines Compendium website', effective date 20 March 2019).

It was noted that findings were identified in relation to delays in publishing updated information on eMC during an internal assessment of updates made during 2018, conducted by the QPPV on 31 December 2018 (report issued on 19 January 2019). A wider impact assessment of the findings was not completed, and corrective and preventative actions did not identify four of the examples cited above (i-iv).

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

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Preventative Action(s)

[redacted]

Finding MA.1 c)

A failure to communicate safety updates to relevant service providers within appropriate timeframes was identified for three of the five safety updates reviewed during the inspection:

i) A Type [redacted] variation to add impulse control disorders to section 4.4 of the [redacted] SmPC (to harmonise with the reference product information) was approved on 07 November 2018, however communication was not sent to iSafety and ProPharma until 21 March 2019.
ii) A Type [redacted] variation to add a warning to sections 4.4 and 4.8 of the [redacted] SmPC regarding autoimmune hepatitis (following a PRAC recommendation) was submitted on 05 November 2018, however communication was not sent to iSafety and ProPharma until 30 January 2019.
iii) A Type [redacted] variation to add a warning to section 4.4 of the [redacted] SmPC regarding aortic aneurysms (following a PRAC recommendation) was submitted on 12 December 2018, however communication was not sent to iSafety and ProPharma until 08 January 2019.

[redacted] 'Maintenance of SmPCs and PILs on the electronic Medicines Compendium' (effective date 20 March 2019) section 5.1.3 stated that the Regulatory Affairs Manager forwards the approval notification along with the approved documents to various personnel including the medical information service provider and pharmacovigilance service provider. ProPharma were contracted for medical information services, and iSafety were contracted to complete pharmacovigilance activities for Dr Reddy's Laboratories. The SOP did not state a timeline in which updates should be communicated; however, it is the expectation of the MHRA that the same timeline for updating the eMC of 10 working days also applies for communicating safety updates to relevant service providers.

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[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]	

Finding MA.1 d)

The following deficiencies related to written procedures for the maintenance of reference safety information were identified:

i) Dr Reddy's did not have a written procedure to describe the critical process of identifying relevant safety conclusions from assessments and recommendations, i.e. by the monitoring of EMA and CMDh websites.

ii) Section 1.0 of [redacted] (SmPC safety updates) stated that the procedure only covered updates to section 4 of the SmPC, however during the inspection, it was confirmed verbally that updates to other sections of the SmPC, such as section 5, would follow the same procedure. There were no other company procedures documenting the process of updates to other sections of the SmPC.

iii) Change control requests were used to track the status and implementation of updates to the product information. Section 5.15 of [redacted] Implementation of Artwork Changes (effective date 06/02/2018) stated that the change control should be closed once the packed artworks have been checked against the approved artwork on the Zen system and implemented. Zen was a web-based artwork approval system used for production and control of print ready artworks. Evidence was provided showing that change control requests were closed prior to implementation:

- [redacted] change control relating to [redacted] (PL [redacted] was closed on 26/11/2018, however the updated PIL is yet to be implemented into packs. To note, this change control relates to the out of date PIL issue described in MA.1b.
- [redacted] change control relating to [redacted] was closed on 09/09/2019, however the updated PIL is yet to be implemented into packs. It is acknowledged that the last batch containing the superseded version of the PIL was certified on 10 May 2018 well in advance of the due date for implementing the updates (due on 05 May 2019).

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]

[redacted]	

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[redacted]

MA.2 Periodic safety update reporting

Requirements:

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

The Human Medicines Regulations 2012,
Regulation 191(1) *"The holder must submit reports known as periodic safety update reports ("PSURs") in relation to the product to the EMA in accordance with this regulation"*

VII.B.6. Quality systems for PSURs at the level of marketing authorisation holders
"Marketing authorisation holders should have in place structures and processes for the preparation, quality control, review and submission of PSURs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the marketing authorisation holder's quality system"

"An appropriate quality system should be in place in order to avoid failure to comply with PSUR requirements such as:
• non-submission: complete non-submission of PSURs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the competent authorities); […]
• poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardised medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;" […]
"Any significant deviation from the procedures relating to the preparation or submission of PSURs should be documented and the appropriate corrective and preventive action should be taken. This documentation should be available at all times."

Finding MA.2 a)

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Dr Reddy's had failed to meet the legal requirement to submit PSURs for two active substances as laid out in Directive 2001/83/EC as amended.

i) The MAH had failed to submit the PSUR for [redacted] covering the period from 01 March 2015 – 28 February 2018, which was due to be submitted by 29 May 2018. It is noted that the PSUR covering the previous interval (01 March 2013 – 28 February 2015) had been submitted to EMA on 15 May 2015. The product had been authorised in the UK since 14 March 2011 based on an Article 10c informed consent application [redacted] For [redacted] products authorised on this legal basis, the 3-yearly submission of PSURs mandated by the list of European reference dates (EURD list) applied.

ii) No PSURs had been submitted for [redacted] to 2019 even though they had been required in the previous four years. In accordance with the EURD list, PSURs were required to be submitted annually for this this active substance. Dr Reddy's portfolio contained 13 marketing authorisations (MAs) for [redacted] in Germany and the UK. 12 of these MAs were authorised based on an Article 10(1) generic application for which no PSURs were required, however the marketing authorisation for [redacted] (MA number [redacted] was approved in Germany on 12 November 2014 based on an Article 10(3) hybrid application. For [redacted] products authorised on this legal basis, the annual submission of PSURs applied.

The deviation from the requirements to submit PSURs for [redacted] was not documented when it was identified together with appropriate corrective and preventive action to be taken (please refer to finding MA.3f).

[redacted]

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[redacted]

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[redacted]

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Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

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

Finding MA.2 b)

The following deficiencies were identified in relation to the content of the [redacted] PSUR (interval 27 May 2015 to 03 August 2017):

i) Section 5.2.3 Other Post-Authorisation Use - Off-label Use incorrectly stated that *"No reports of associated with the off-label use of [redacted] were received during the review period"*; however, two cases reporting off-label use had been received in the interval period [redacted] initially received on 04 February 2016 and 15 February 2017 respectively). It is acknowledged that the PSUR Executive summary and section 18.2 Benefit-Risk Analysis Evaluation stated that there were *"two case reports of off-label use"* but no further information on the nature of the off-label use was provided in these sections.

ii) Appendix 2 'Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials', and 'Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Drug Reactions From Post-Marketing Data Sources', did not include the adverse reactions of anxiety and depression associated with case [redacted] a literature case from the US received on 11 June 2015, as the co-suspect drug [redacted] had been erroneously coded in the safety database using the WHO dictionary rather than the company dictionary, when [redacted] could not be excluded as a company drug. As a result, the drug was coded incorrectly as a non-company drug and was excluded in the output used for construction of the summary tabulation.

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[redacted]

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[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 c)
There were no instructions in written procedures to define the search criteria used to identify relevant cases for discussions in PSUR subsections (e.g. medication errors, off-label use etc.) of the PSUR. In response to a specific document request concerning the process for identifying cases for specific discussion in the PSUR, Dr Reddy's confirmed that the Excel case output used for the PSUR summary tabulations was reviewed, however there was no documented guidance as to how this spreadsheet was screened or filtered, including the selection of specific PT or SOC terms.
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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MA.3 Quality management system

Requirements:
Directive 2001/83/EC as amended, Article 104(2) Commission Implementing Regulation (EC) 520/2012, Article 4(3) *"Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved."* Article 13 *"1. Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness. […]*

2. Corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary."

GVP Module IV.B.2.1. Strategic level audit planning

IV.B.2.4. Actions based on audit outcomes and follow-up of audits

IV.C.2.1. Reporting by the marketing authorisation holder
"Based on the audit findings, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented."

GVP Module I.B.6. Responsibilities for the quality system within an organisation
"For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for: […]
identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;"

I.B.11.Documentation of the quality system

I.B.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

The Commission Implementing Regulation (EC) 520/2012 describes the principles in Article 8, for the quality system that MAHs must establish, to be adequate and effective for the performance of pharmacovigilance activities. This is to based on aspects including "*quality and control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out*", and "*quality improvements: correcting and improving the structures where necessary*".

Dr Reddy's had failed to implement a quality system that fully addressed these aspects in that non-compliance that was identified through audits (MA3a), assessments (MA3b) and monitoring activities (MA3c) was not effectively addressed. In addition, deficiencies were identified with the pharmacovigilance audit programme (MA.3d), the monitoring of audit CAPA implementation (MA3e) and the recording of unplanned deviations from pharmacovigilance procedures (MA3f).

Finding MA.3 a)

Dr Reddy's had failed to effectively resolve non-compliance identified through internal audits of the pharmacovigilance system.

From an internal audit of the pharmacovigilance system in 2014, major findings were reported in relation to the availability of information relating to the global pharmacovigilance system for Dr Reddy's products authorised in the EU and in relation to having measures in place to monitor the effectiveness of meeting defined deadlines for the update of product safety information.

In 2017, a subsequent internal pharmacovigilance audit reported a critical finding for 'CAPA management', including the failure to implement the CAPA from the 2014 audit.

The following deficiencies in the management of these audit findings were identified by inspectors:

i) No root cause analysis and impact analysis of the findings reported in 2014, or plan detailing the corrective and preventative actions to address these findings as required by GVP Module IV could be provided to inspectors.

ii) There was no root cause analysis and impact analysis to support the proposed CAPA plan to address the critical finding reported in 2017. Furthermore, this plan did not address the finding for 'CAPA management', which had been cited against the requirements in GVP module IV for effectively addressing audit outcomes and systematically tracking of implementation of agreed actions, instead it focussed solely on the implementation of the regulatory information management tracking system.

At the time of this MHRA inspection, the major findings from 2014 remain unresolved as reported in findings MA.1 (deficiencies and delays in updating product safety information), MA.4 (inaccurate information concerning the global pharmacovigilance system in the PSMF) and the finding for 'CAPA management' in 2017 has not been addressed as reported in finding MA.3d (regarding a lack of formal mechanisms for CAPA management and escalation).

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.3 b)

The pharmacovigilance audit programme did not provide coverage for the global pharmacovigilance system. The risk assessment conducted to generate the audit programme was not comprehensive for all relevant aspects of the global pharmacovigilance system.

[redacted] Pharmacovigilance quality control and auditing' (effective 01 February 2018) stated that *"systems, processes, vendors and partners identified for audit or assessment"* included in the risk assessment used to draft the strategic and tactical audit plan however, there was no instruction on how entities for inclusion in the risk assessment within these criteria would be identified. It was stated in response to document request P6 that Annex B of the PSMF was used to compile the list of partners for audit risk assessment, however the audit programme was limited to European affiliates, processes and entities, and the following entities were not included in the risk assessments used to prepare the current tactical audit plan (dated 30 Sept 2019):

- The EU partner [redacted] with whom Dr Reddy's had an agreement for own label supply and an SDEA effective from 26 July 2018
- Partners and affiliates in India and emerging markets
- Partners in North America
- The service provider iSafety, responsible for conducting critical pharmacovigilance processes for ICSR management and PSUR production, based in India, was not included in the risk assessment of service providers for audit

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

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

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

Finding MA.3 c)
The tracker used to monitor the compliance of safety variation submissions [redacted], dated 14 October 2019) recorded 29 individual variations as late. On request of evidence during the inspection to demonstrate action taken as a result of the late

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submissions, comments were provided that gave possible explanations for causes, however there was no evidence that analyses of the root cause or impact had been conducted and whether corrective and preventative measures should be implemented. To note, the implementation of safety variations is a defined key performance indicator in the PSMF, with a target of 100% submissions on time (defined as being submitted within 120 days in SOP [redacted] unless otherwise stipulated). The tracker clearly indicated that the 100% target had not been met, however no further action has been taken.

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 MA.3 d)

Dr Reddy's did not have a process to systematically monitor the implementation of agreed actions to address audit findings.

i) Annual audit and assessment trackers were used to track when audits were conducted, and closed together with a summary of the findings, the status of the finding and the dates each finding was considered 'closed', however there was no written instruction on how to use these trackers and the trackers did not track the actions associated with audit findings.

ii) There was no formal mechanism to escalate any delays to implementing CAPA. 'Policy on pharmacovigilance quality assurance for Dr Reddy's Europe Generics' rev 2 dated January 2017 stated that *"In the event of any conflict of interest between auditor and auditee/assessor and assessee, e.g. non-completion of corrective action*

plans, there will be an escalation process to the appropriate EEA QPPV and/or Senior Management." However, there was no documented process for this escalation mechanism.

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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 MA.3 e)

There was no mechanism for recording unplanned deviations from pharmacovigilance processes at Dr Reddy's and therefore the requirements to document such deviations in the PSMF until resolved could not be met.

It was acknowledged that such a procedure existed at the service provider iSafety and deviations to iSafety processes would be recorded in the iSafety quality system.

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]

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

MA.4 Pharmacovigilance system master file

Requirements:

GVP Module II.B.6. Pharmacovigilance system master file presentation
"The information [in the PSMF] shall be succinct, accurate and reflect the current system in place"

II.B.4.2. PSMF section on the organisational structure of the marketing authorisation holder
"Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided."

II.B.4.8. Annex to the PSMF
"For marketing authorisations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs."
"The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation: […]

- *the presence on the market in the EU […]*
- *other (non EU) territories where the product is authorised or on the market."*

Finding MA.4 a)

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The presentation of links with other organisations in the annex of the PSMF was misleading and inaccurate.

[redacted] Safety data exchange agreements' [redacted] effective date 01 October 2017) described a system of using five different SDEA templates (named [redacted] with business partners. The circumstances in which each template type should be used were defined within the templates.

The [redacted] template included the following statement regarding the responsibilities of the business partner ('COMPANY'):

> *"This template is applicable for the following scenario:*
> *The COMPANY holds the MA(s) in the territory(s). The MA(s) may be entire DC or MR procedures or national-only. These are wholly independent of any Dr. Reddy's MAs for the same active.*
> *The COMPANY is responsible for all pharmacovigilance activities for the product(s). Dr. Reddy's may be the supplier of the product and also hold independent MAs in the Territory."*

The template types were applied inconsistently and led to the misrepresentation of partner and associated pharmacovigilance responsibilities in the PSMF. For example:

- Annex B incorrectly stated that a Type II SDEA was in place with partner [redacted] with whom Dr Reddy's had a 'Licensing & supply' contract for three products, [redacted] in Germany and Austria. This Type of SDEA indicated that Dr Reddy's had no pharmacovigialnce respobnsibilities for these products in these territories, however according to the contracts in place between Dr Reddy's and [redacted] pharmacovigilance responsibilities were assigned to Dr Reddy's.

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[redacted]

Further Assessment

[redacted]

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[redacted]

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

Finding MA.4 b)

There were links with other organisations in the PSMF that were missing or that had been incorrectly included without further information regarding cross referenced PSMFs.

i) SDEAs were incorrectly included in the PSMF without a corresponding cross-referenced PSMF. The following examples of contracts where Dr Reddy's did not have pharmacovigilance responsibilities were incorrectly included in Annex B:

- Partner [redacted] who hold MA for [redacted] in Austria, where Dr Reddy's perform batch release.
- [redacted] had an own label supply agreement with Dr Reddy's for [redacted] in Croatia. Dr Reddy's confirmed to the inspection team that [redacted] resided in [redacted] though this other PSMF was not cross referenced in the PSMF.

A cross reference should be included to the partner PSMF that describes the pharmacovigilance system for products where Dr Reddy's is not MAH and Dr Reddy's is performing only some pharmacovigilance activities. If Dr Reddy's is not MAH for the product and has no pharmacovigilance responsibilities for the product, the contract should not be included within Dr Reddy's PSMF.

ii) Annex B also incorrectly contained agreements with partners for active substances that were not authorised in the EU, specifically:

- [redacted] in Argentina regarding [redacted]
- [redacted] in Jordan regarding [redacted]
- [redacted] in South Korea regarding [redacted]
- [redacted] in South Africa regarding [redacted]
- [redacted] in India, Myanmar, Nepal and Sri Lanka regarding [redacted]

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Root Cause Analysis
[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

Finding MA.4 c)

Examples were identified where Annex H did not accurately present all territories where EU authorised medicinal products were authorised or on the market, specifically:

i) Annex H stated 'n/a' for the launch date of [redacted] in Germany, however, according to the [redacted] PSUR (DLP 03 Aug 2017), both products were launched in Germany on 15 July 2015.

ii) [redacted] were supplied in Costa Rica, Guatemala, Nicaragua, El Salvador, Panama, Honduras, the Dominican Republic and Paraguay through an own-label contract with VMG Pharma (signed August 2016). However, although this agreement was correctly presented in Annex B, these countries were not listed for these products in Annex H.

iii) During the inspection it was confirmed by the MAH that EU authorised Dr Reddy's products [redacted] were also authorised in Kuwait, however this was not presented in Annex H.

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]	

Finding MA.4 d)

Annex G of the PSMF did not include all audits of the global pharmacovigilance system. The following audits of the US pharmacovigilance department were not included in the list of audits conducted and the planned audits:

i) The pharmacovigilance internal audit conducted of the Dr Reddy's Laboratories Ltd. US affiliate's pharmacovigilance department on 06-10 March 2017.

ii) The tactical audit plan included in Annex G did not include the planned audit of pharmacovigilance (reference [redacted] scheduled for 10-11 December 2019 from the North America Princeton office internal audit schedule for 2019.

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]

MA.5 Risk management plans

Requirements:

Commission Implementing Regulation (EC) 520/2012,
Article 32(1) *"Where the marketing authorisation holder updates a risk management plan, it shall submit the updated risk management plan to the national competent authorities or the Agency as appropriate. After agreement with the national competent authorities or the Agency as appropriate, the marketing authorisation holder may submit only the modules concerned by the update."*

Finding MA.5

The MAH did not submit the updated RMP for [redacted] o MHRA for approval after the list of safety concerns was updated in RMP section [redacted] between version [redacted] dated 05 January 2015) and v1.2 (dated 22 December 2015). The following changes were made:

i) Removal of the important identified risk of [redacted]

ii) Removal of the important potential risk of upper gastrointestinal tract (UGIT) bleeding events with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs)

iii) Removal of the following missing information:
- Characterisation of the safety and tolerability of [redacted] in paediatric patients
- Long-term safety data in chronic pain patients
- Characterisation of drug utilisation in unapproved indications and populations

In addition, the missing information on *"Safety of duloxetine in elderly patients ≥ 75 years old with concomitant NSAIDs use"* was replaced with *"Use of [redacted] in elderly patients".*

RMP [redacted] (signed 22 December 2015) was updated and submitted to [redacted] at the time of submission of the marketing authorisation application (MAA) for the [redacted] which was granted on 03 August 2016.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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

MA.6 Signal detection

Requirements:

GVP Module IX.B.2. Signal detection
"Signal detection should follow a methodology which takes into account the nature of data and the characteristics (e.g. time on market, patient exposure, target population) as well as the type of medicinal product concerned (e.g. vaccines and biological medicinal products may for example require specific methodological strategies [...] The signal detection process should be adequately documented by each organisation"

Although not reviewed in detail during this inspection, the following deficiency was identified regarding signal detection, during the review of data used to compile the most recent PSUR for duloxetine.

Finding MA.6

Events meeting the criteria defined by Dr Reddy's for detecting potential signals had not been reviewed during signal detection activities for [redacted]
In the annual signal detection covering the period from 01 January 2016 to 31 January 2016 that was completed on 16 January 2017, 26 adverse event preferred terms (PTs) met the threshold of an absolute number ≥3, however these were not further reviewed as described in the SOP effective at the time, with the rationale documented in the review *"due to the large data set"*.

SOP [redacted] Signal management (version [redacted] effective date 01 July 2016) defined a the criteria for events to be reviewed further in section 5.1.2. Signal detection and evaluation:

- Terms with an absolute number ≥3 or frequency ratio ≥3 in the in the interval period
- Terms in the Close Monitoring list
- Medically significant events reported for the first time

Out of the 26 PTs, two (contusion and nightmare) were not included in the EU SmPC. The

PT of drug interaction also met this threshold but had not been reviewed further to establish if the reported interactions were involving the same suspect drugs.

This finding has been graded as major due to the failure to investigate the potential signals meeting criteria defined by the methodology employed by the MAH. The rationale documented by the MAH is not considered adequate by the inspectors as no further actions were proposed or taken to perform any validation of any of the potential signals in this dataset.

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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]	

C.4.3 Minor findings

MI.1 Oversight of the pharmacovigilance system by the Qualified Person for Pharmacovigilance

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Finding MI.1 a)
There was no procedural or contractual documentation describing the monthly meetings between Dr Reddy's and the pharmacovigilance service provider iSafety. These monthly teleconferences were described in the PSMF [redacted] dated 21 October 2019, p8) as a mechanism of oversight by the MAH; however, these were not formalised by written procedures or in contractual agreements, such as the service agreement with iSafety (effective date 31 January 2019). The MAH verbally described that the purpose of these meetings was for the service provider to provide an update on the ongoing work for all territories in which they provide pharmacovigilance services and review any concerns from the MAH for example, on quality of work.
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 MI.1 b)
There was no procedural documentation describing the mechanisms that Dr Reddy's had put in place to oversee the case processing activities carried out by iSafety. The EU PV team carried out a 100% quality check of all spontaneous cases once they had been fully processed in the safety database and prior to submission to EudraVigilance. Other case types were checked randomly; however, the frequency and sample size of these checks was not documented. It was verbally stated that these checks occurred very often at the beginning of the iSafety service agreement (effective date 31 January 2019), but the frequency was now reduced as the case quality had improved.
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]

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

Finding MI.1 c)

Monthly reports were prepared for the EU, North America, and India and the Emerging Markets as a tool to provide an overview of pharmacovigilance activities and monitor their compliance in each of the regions. The following deficiencies were noted in relation to the monthly reports:

i) No monthly report summarising pharmacovigilance activities in North America was available for January 2019.

ii) The monthly reports summarising pharmacovigilance activities in India and the Emerging Markets in January and February 2019 had not been shared with the EU QPPV and the EU PV team at the time of their preparation. It is acknowledged that the information was retrospectively provided to the QPPV on 26 August 2019 as part of a cumulative report covering the period from January to June 2019.

[redacted] Compliance and Quality Monitoring (revision 01, effective date 21 December 2017) stated in section 3 'Management reporting':

"[Global Head of Pharmacovigilance] *Presents the monthly compliance report at the monthly Global Medical Affairs meeting and sends the final monthly management report to:*

- *Pharmacovigilance Heads/Leads of Regions*
- *Global Head of Medical Affairs".*

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]

MI.2 Collection and collation of ICSRs

Finding MI.2 a)

Incorrect limits were applied to the download of ISCRs from EudraVigilance.
In relation to the download of ICSRs from competent authorities, the MAH only searched for cases from the UK, Germany, Romania, France, Spain and Italy. However, according to PSMF Annex H, the MAH also held marketing authorisations in the Netherlands and Denmark (but these were listed as not launched yet).
In addition, the Reporting Matrix [redacted] dated 30 September 2019), an Excel spreadsheet detailing all product licences in the EU and the rest of the world, associated additional PV activities and aRMMs as well as the partners with whom an SDEA was in place, showed that the MAH held a marketing authorisation in Hungary for [redacted]

A search in EudraVigilance was run by inspectors to identify if there were any potential competent authority ICSRs for these countries and active substances. A search on [redacted] ICSRs from Hungary identified two reports submitted by the competent authority which reported adverse reactions with an unspecified [redacted] product.

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]	

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Finding MI.2 b)
There was no established mechanism for physicians performing medical review at iSafety to request follow-up. Although Dr Reddy's procedure [redacted] Global ICSRs management: post-marketing' [redacted] effective date 28 July 2017) included the provision for physicians at medical review to follow-up cases, the service provider iSafety [redacted] 'Overview of Individual Case Safety Reports (ICSR)[redacted] effective date 04 October 2019) used by the service provider conducting ICSR management did not include a process physicians should follow at the medical review stage if further information was required to perform an assessment of the case.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

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

D.2 Recommendations

The MAH is encouraged to share this inspection report with relevant service providers to whom it has sub-contracted pharmacovigilance activities. Service providers are reminded that deficiencies that are more broadly applicable to MAHs not subject to this inspection may need to be shared with those affected, such that appropriate CAPA can be derived. The service provider and MAH(s) affected should be able to demonstrate effective assessment and resolution of deficiencies that have been reported during any inspection.

Given the seriousness of the inspection findings, the Inspection Action Group for GCP and Pharmacovigilance (IAG) has recommended that the next MHRA pharmacovigilance inspection is performed within the next 12-18 months, to review the impact of the actions taken in response to the inspection findings. Please note that this inspection may be conducted unannounced or at short notice.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- Official Journal of the European Union, 2013/C 223/01, Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures
- EMA Q&A - List for the submission of variations according to Commission Regulation (EC) 1234/2008

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Dr Reddy's	**DATE**	16 October 2019
LOCATION	Remote review	**START TIME**	9.00am

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Day one of the inspection will be conducted remotely through document review by inspectors.	-	Ad hoc TCs may be required for queries during the day in relation to any topic listed on the plan.
The Inspection Plan may need to be amended during the inspection. Some interview sessions may be held in parallel. [redacted]		

MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Dr Reddy's	**DATE**	21 October 2019
LOCATION	Dr Reddy's Laboratories (EU) Ltd, 410 Cambridge Science Park, Milton Road Cambridge, CB4 0PE	**START TIME**	9.00am for 9.30am start

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system, the quality system and areas undergoing remedial activities *(approx. 20 minutes)* Please additionally prepare a short presentation overview of the project to develop and implement a global regulatory and information management system.	[redacted]	[redacted]
Document review	-	Inspectors only
Quality assurance To include an overview of the processes for: - Audit scheduling - Management of CAPA from audits - Deviation management	[redacted]	[redacted]

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LUNCH	-	-
Spontaneous sources of safety information - Medical information and quality complaints - Management of SDEAs - Maintenance of PSMF Annexes B and C	[redacted]	[redacted]
Maintenance of reference safety information - Identification of required updates from all sources - Submission of safety variations - Implementation of approved updates to product information including SmPC, patient information leaflets and websites	[redacted]	
Document review	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Dr Reddy's	**DATE**	22 October 2019
LOCATION	Dr Reddy's Laboratories (EU) Ltd, 410 Cambridge Science Park, Milton Road Cambridge, CB4 0PE	**START TIME**	9.00am

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review	-	Inspectors only
Periodic safety update reports - Scheduling, production, quality control and submission.	[redacted]	[redacted]
Management of spontaneous ICSRs Including but not limited to: - Case processing - Expedited reporting to EudraVigilance - ICSR follow-up activities including the sending of targeted questionnaires	[redacted]	[redacted]
LUNCH	-	-

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Oversight of the pharmacovigilance system by the QPPV and marketing authorisation holder Specifically including: - Oversight of the third-party service provider - Oversight and compliance management of risk management plan commitments	[redacted]	[redacted]
Document review	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Dr Reddy's	**DATE**	23 October 2019
LOCATION	Dr Reddy's Laboratories (EU) Ltd, 410 Cambridge Science Park, Milton Road Cambridge, CB4 0PE	**START TIME**	9.00am

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review and ad hoc interview sessions as required	-	Inspectors only
LUNCH	-	-
Document review and ad hoc interview sessions as required	-	Inspectors only
Inspectors meeting	-	Inspectors only
Closing meeting	-	All welcome

APPENDIX III POST INSPECTION DOCUMENTATION

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