Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Eli Lilly & Company Limited

MHRA Inspection Number: Insp GPvP 6/24884-0006

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
DME	Designated Medical Event
EMA	European Medicines Agency
eRMR	Electronic Reaction Monitoring Report
EU	European Union
EVDAS	EudraVigilance Data Warehouse and Analysis System
GPS	Global Patient Safety
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IME	Important Medical Event
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorisation Safety Study
PC	Product Complaint
PSMF	Pharmacovigilance System Master File
PSP	Patient Support Programme
PSUR	Periodic Safety Update Report
PRR	Proportional Reporting Ratio
PV	Pharmacovigilance
QPPV	Qualified Person responsible for Pharmacovigilance
SAE	Serious Adverse Event
SDR	Signal of Disproportionate Reporting
SST	Safety Surveillance Team
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Eli Lilly, MFL6
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	22 – 23 June and 06 – 08 July 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	22 – 25 September 2015 01 – 05 August 2011 20 – 24 August 2007 22 – 26 March 2006
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	Inspection focused on two centrally authorised products: [redacted]
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Lilly Safety System – web-based application based on Oracle Argus software
Key service provider(s):	The majority of key pharmacovigilance activities were performed in-house by the MAH. [redacted] provided vendor services for local Patient Support Programmes [redacted] Corrona-managed patient registries were utilised for non-interventional studies [redacted]
Inspection finding summary:	2 Major findings 4 Minor findings
Date of first issue of report to MAH:	06 August 2020
Deadline for submission of responses by MAH:	11 September 2020 Clarifications due 09 October 2020
Date(s) of receipt of responses from MAH:	11 September 2020 Updated responses received 09 October 2020
Date of final version of report:	13 October 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Eli Lilly 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 Regulation 726/2004/EC as amended, 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.

Eli Lilly (hereafter Lilly) is a global innovator pharmaceutical company, headquartered in Indianapolis, USA. Global pharmacovigilance activities are managed by the Global Patient Safety (GPS) organisation whose principal locations are at the Lilly Corporate Centre in Indianapolis, USA, the Lilly Research Centre in Erl Wood, UK and the Eli Lilly do Brazil in Sao Paulo, Brazil, with additional regional centres located in India and Japan.

Lilly's product portfolio consists of centrally authorised products (CAPs) and nationally authorised products (mutual recognition and decentralised procedures) indicated for a wide range of therapeutics areas, including oncology, endocrinology, immunology and neuroscience.

At the time of the inspection, the PSMF was located in Bad Homborg, Germany, which is also the site of the EU QPPV.

B.2 Scope of the inspection

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The inspection included a review of the global pharmacovigilance systems and was specific to two CAPs, [redacted]

Due to Covid-19, the inspection was performed remotely. No formal interview sessions were scheduled, with the inspection primarily taking the form of document review (including outputs from the global safety database). Ad hoc teleconferences were held with subject matter experts as necessary. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

Areas of risk management, including the maintenance of reference safety information and additional risk minimisation activities, were not reviewed during this inspection 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 (version 32.1, 27 April 2020) 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, details of which are contained within document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. Minor amendments to the Inspection Plan that occurred during the inspection are highlighted using italic text in Appendix II.

A closing meeting was held via teleconference to review the inspection findings on 08 July 2020.

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

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

Since the previous MHRA inspection in 2015, the company had made the following changes to the pharmacovigilance system:

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- In March 2019, there was change in the EU QPPV to [redacted] who is based in Germany.
- The location of the EU PSMF was subsequently updated in August 2019 from the Erl Wood site in the UK to the site of the EU QPPV in Germany.
- Introduction of an artificial intelligence (AI) system (MosaicPV) used for case intake in June 2018. The current use of MosaicPV is limited by product, geography and particular Global Patient Safety personnel.

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

No critical findings were identified from the review of pharmacovigilance processes, procedures and documents performed during this inspection.

C.4.2 Major findings

MA.1 Periodic safety update reports

Requirements:

Commission Implementing Regulation (EU) No 520/2012,
Article 34(1) *"The periodic safety update report shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last periodic safety update report."* (emphasis added)

GVP Module VII – Periodic safety update report (Rev 1)
VII.B.5.6. PSUR section "Data in summary tabulations"
"The objective of this PSUR section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other noninterventional solicited source."

Periodic safety update reports (PSURs) provide an evaluation of the current understanding and the risk-benefit balance of a medicinal product. The following finding was noted in relation to the inclusion of data in PSURs:

Finding MA.1 a)

The PSUR search logic used to extract post-marketing solicited cases for all aspects of PSUR writing, including the summary tabulations, incorrectly excluded a subset of cases from the PSURs. As a result, the assessment of PSURs was not based on all available data.

For the post-marketing solicited case types 'PSP, Market Research, Individual Patient Use and Other Solicited', the PSUR searches only retrieved cases where the primary suspect product was the subject of the PSUR. For example, if a PSP case had a primary product X and a co-suspect company product Y, product X PSUR searches would retrieve cases for product X; however, product Y PSUR searches would not retrieve the case as product Y was not the primary product.

This logic had been present in the PSUR search strategy since June 2013. Preliminary assessment conducted by the company to identify relevant cases that had a co-suspect drug and met PSUR inclusion criteria across the entire product portfolio for the period June 2013 to July 2020 identified approximately 300 PSP cases that had not been included in the respective PSURs. Of these 300 cases, there were no cases for [redacted]

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The company confirmed that these 300 cases had qualified for inclusion in the post marketing routine surveillance reports for the respective suspect product and had been reviewed as part of routine surveillance.

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]	

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[redacted]

MA.2 Management and reporting of adverse events and reactions

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media
"In relation to cases from the internet or digital media, the identifiability of the reporter refers to the possibility of verification of the existence of a real person based on the information available e.g. an email address under a valid format has been provided (see VI.B.2. for ICSRs validation)."

VI.B.2. Validation of report
"Four minimum criteria are required for ICSRs validation: […]

a. one or more identifiable reporter, (see VI.A.1.4. for primary source definition), characterised by parameters such as qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional), name, initials, or address (e.g. reporter's organisation, department, street, city, state or province, postcode, country, email, phone number). […]
In line with ICH-E2D, the term 'identifiable' indicates that the organisation notified about the case has sufficient evidence of the existence of the person who reports the facts based on the available information.

d. one or more suspected adverse reaction […]
The report also does not qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information on the type of adverse reaction. Similarly, the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product […]

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission as ICSR. Competent authorities and marketing authorisation holders are expected to exercise due diligence in following-up the case to collect the missing data elements and follow-up activities should be documented."

VI.B.3. Follow-up of reports
"When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy (see VI.B.6.1. for guidance on the management of pregnancy reports), cases notifying the death of a patient, or cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum criteria for reports validation […].

Similarly, for suspected adverse reactions related to biological medicinal products, the definite identification of the concerned products with regard to their manufacturing is of

particular importance. Therefore, all appropriate measures should be taken to clearly identify the names of the products and their batch numbers."

GVP Product- or Population-Specific Considerations II: Biological medicinal products
P.II.B.2. Management and reporting of adverse reactions
"A follow-up procedure should be put in place to obtain the batch number where it is not indicated in the initial report."

The following findings were noted in relation to the management and reporting of adverse events (AEs) and adverse drug reactions (ADRs):

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Finding MA.2 a)

The MAH had incorrectly submitted cases to EudraVigilance that reported the outcome of death only with no further information and no indication of a possible causal relationship. The following examples were identified:

- Case [redacted] Solicited report from the UK received on 31 May 2019 via a baricitinib PSP vendor and reported to EudraVigilance on 10 June 2019. Source documentation stated, *"Patient has sadly passed away"*, with reporter causality to baricitinib stated as "*Don't know*" and company causality negative.

- Case [redacted] Spontaneous report from the US received on 07 May 2019 via the sales force and reported to EudraVigilance on 15 May 2019. Source documentation stated, *"Reporter stated she is not sure if the patient was taking* [redacted] *but did see enrollment papers. Reporter stated she is not too clear on information and did not ask for details but when she inquired about patient's enrollment papers reporter was informed that the patient died about 2 days ago. No further information provided."* In the Adverse Event/Product Complaint (AE/PC) Collection Form under event details, death was reported with 'unknown' populated for the question 'was this event related to the drug?'.

- [redacted] - Spontaneous report from the USA initially received on 07 May 2019 via the sales force. Follow-up information was received on 03 June 2019 and the case was subsequently reported to EudraVigilance on 10 June 2019. Initial source documentation stated "*Caller stated the nurse reported that they had a patient on* [redacted] *that passed away. Caller stated the nurse reported they received a call on February 19th from the patient's daughter stating the patient passed away the week before […] Caller stated she asked what the cause of death was. Caller stated the nurse reported they didn't have any additional information and that they did not believe the death was related to the* [redacted] Further information was requested on 10 May 2019 in which the reporter was requested to answer the questions in the mortality spontaneous follow-up form. The information provided confirmed that the date of death and the underlying cause was unknown, with an explanation stating, "*patients daughter contacted office […] to inform us that patient passed away the week before*". The answer selected to the question 'Is the reported cause of death related to drug?' was 'unknown'.

Section 5.1.2. of [redacted] 'Expedited Reporting at the Erl Wood Regional Centre' (version 23.0, 01 March 2018) stated "*In general, death not otherwise specified (NOS) is considered an outcome, not a reaction, and therefore should not be submitted […] For spontaneous cases, there must be a positive causality (Yes or Unknown) between the death and the Lilly suspect drug to be considered for reporting."*

During the inspection, 10 spontaneous cases were identified for ixekizumab and baricitinib reporting the outcome of death only where reporter causality had been assessed as unknown, which had been submitted to EudraVigilance.

A causality assessment of 'unknown' in cases reporting an outcome only does not indicate a possible causal relationship with the suspected medicinal product and hence these reports are not valid and should not be submitted to EudraVigilance. To note, where a causality assessment was 'not reported', a positive causality was not assumed, and the cases were not reported to EudraVigilance.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 b)
Procedural documents contained stricter ICSR validity requirements for digital media reports than were outlined in GVP Module VI.B.2., in relation to determining whether there was an identifiable reporter. This resulted in cases that were not submitted to EudraVigilance despite containing the four minimum criteria required for ICSR validation.

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A serious report [redacted] was received via the [redacted] Facebook page on 30 March 2020 reporting "*heart failure*". The company responded to the post on 31 March 2020, stating to inform a doctor and providing a telephone number for the Lilly Answers Center. The reporter subsequently responded to the post on 31 March 2020 and stated, "*his Dr does know…he now has a pace maker!!!!*". By responding to the company via their post on social media, the reporter was demonstrably identifiable.

However, Lilly procedure 'Valid Case' [redacted] 20 December 2019) stated that for digital media reports "*The reporter is considered valid only if contactable (that is, valid only if reporter telephone number, address, or email address is provided).*" As the reporter in the above example had not provided an address, email address, or telephone number, the report was considered non-valid and had not been reported to EudraVigilance. To note, the reported event in this example was an important potential risk of the suspect drug [redacted]

This process was not considered to be in line with GVP Module VI, which considers a reporter to be 'identifiable' if there is sufficient evidence of the existence of the person based on the available information. In GVP Module VI.B.1.1.4. for digital media reports, an email address under a valid format is given as an example of available information that could be used to verify the existence of a real person. However, it is not considered appropriate to limit validation of reporters to only those that can be contacted via phone, post or email.

For company-sponsored forums, such as product-specific social media pages, where there is clear evidence of engagement from patients/reporters, a more conservative approach should be taken with regards to ICSR validity requirements.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 c)
The following deficiencies were identified in relation to the request for follow-up information of adverse event reports: • There were examples of cases received via a PSP vendor where it was not known if permission to follow-up with the reporter had been requested, and as such no follow-up was pursued by the UK affiliate: ○ Case [redacted] Solicited report from the UK received 22 November 2018 via an [redacted] reporting the outcome of death only with no further information or causality provided. It was not clear if the reporter had provided consent to follow-up, and as such no follow-up requests had been sent to obtain further information on the cause of death and the

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reporter assessment of causality/relatedness to the suspect drug to consider validity of the report for expedited reporting.

- Case [redacted] Solicited report from the UK received 14 November 2018 via an [redacted] vendor (Quintiles), reporting the adverse reaction 'shingles' (herpes zoster). The AE collection form stated that there was no consent to contact the patient; however, healthcare professional (HCP) details had been provided under the contact information. It was not clear if permission had been granted to contact the HCP, and as such no follow-up requests were sent to obtain further information on the important identified risk of herpes zoster.

- Case [redacted] Solicited report from the UK initially received 24 January 2019 via an [redacted] vendor (Quintiles), reporting pregnancy whilst on treatment with [redacted] No follow-up requests were sent to obtain information on the outcome of the pregnancy, as it was not clear if permission to follow-up with the reporter had been given. To note, follow-up information was received spontaneously from the reporter regarding the outcome of the pregnancy on 31 May 2019, in which consent to follow-up was requested and obtained, and follow-up letters were sent by the MAH on 10 June 2019 and 15 July 2019.

- There were examples of cases where follow-up requests had been sent to the reporter but were missing key information:

  - Case [redacted] Spontaneous report from the UK received on 09 November 2018 from a HCP reporting basal cell carcinoma with [redacted] On the AE-PC form, it stated that lot/batch number was 'not asked'. Follow-up requests were sent on 21 November 2018, 03 and 24 January 2019; none of which included a request for the batch number of [redacted] As [redacted] is a biological medicine, there should be a follow-up procedure in place to obtain the batch number where it is not indicated in the initial report in line with GVP Product- or Population-Specific Considerations II: Biological medicinal products.

  - Case [redacted] Solicited report from the UK received on 24 June 2019 via an [redacted] PSP vendor reporting the outcome of death only with no further information or causal association. Follow-up was requested on 27 June 2019, in which the circumstances of death (cause, date, hospitalisation status and autopsy details) and medical history/concomitant medications were requested; however, the MAH had not requested the reporter's assessment of causality/relatedness to the suspect drug to consider the validity of the report for expedited reporting.

This finding is minor in nature as little impact was observed from the sample reviewed during the inspection, and the examples identified appeared to be isolated. It has however been grouped as part of this major finding and a full impact assessment should be completed as part of the responses to the inspection report and suitable CAPA should be proposed.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

- [redacted]

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

C.4.3 Minor findings

MI.1 Signal management

Finding MI.1 a)
As part of Eli Lilly's signal detection methodology, the Proportional Reporting Ratio (PRR)* was utilised on a monthly basis to detect potential product quality issues due to a manufacturing, packaging, distribution, or storage causative factor for all products with at least 500 cases of AE/PCs. This included biological medicinal products, such as [redacted] However, the methodology did not take into account the size of the batch or estimated patient exposure. In the absence of these denominator data, the adverse reaction reporting rate could not be calculated. Although this methodology may be helpful in identifying potential product quality signals for batches that have been on the market for a while, the methodology may not be sensitive enough to detect signals for newer batches recently released to the market. GVP Chapter P-II.B.4. states *"Denominator data and data of suspected adverse reactions (see GVP Module IX) should be analysed to support continuous signal detection and particularly detection of any apparent changes in suspected adverse reaction reporting rates or trends that could indicate new signals (particularly following manufacturing changes)."* **Post-inspection request:** In the inspection response, Eli Lilly is encouraged to describe the scientific rationale for the chosen methodology regarding signal detection for biological medicines, and any proposed changes, in the context of the guidance provided in GVP Chapter P-II. *The PRR is a measure of disproportionality of reporting used to detect signals of disproportionate reporting (SDR). This method makes the assumption that when an SDR is identified for a product-specific batch-to-batch comparison, the suspected AE/PC is reported relatively more frequently with the batch of interest than with all other product batches. The numerical AE/PC surveillance threshold for defining SDRs was PRR ≥ 2.0, n ≥ 5.
Root Cause Analysis
[redacted]

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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 were no documented criteria in Lilly procedural documents for the review of the electronic reaction monitoring reports (eRMRs) from EVDAS for the purpose of monitoring the data available in the EudraVigilance database. Both [redacted] were active substances involved in the pilot on signal detection in EudraVigilance. The criteria used by the GPS Surveillance team for review of the eRMRs were as follows:

1) Important Medical Event (IME) that meets the 'SDR All' or 'Paediatric/Geriatric SDR' threshold
2) IME with a Fatal outcome (regardless of SDR)
3) Designated Medical Event (DME) (regardless of SDR)

There was a procedural document entitled 'Conducting Safety Surveillance in EudraVigilance'

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[redacted] 15 March 2018); however, the criteria utilised when reviewing the data in the eRMR for potential safety signals was not included within this document. It was acknowledged that the review criteria were contained within a training slide deck entitled 'EVDAS – Key Information for Pilot Participants' (dated 23 February 2018).

The monitoring of the available data in EudraVigilance is currently in a pilot phase in the EU. However, it remains a legal requirement for the MAHs involved in the pilot to undertake this monitoring and, therefore, the procedural requirements in Commission Implementing Regulation (EU) No 520/2012 Article 11(1)(a) apply. It is strongly recommended that the review criteria are formalised in an approved and controlled procedural document.

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 MI.1 c)
The Safety Surveillance Team (SST) for [redacted] met on a monthly basis to review routine AE and literature data, along with any available study reports. The SST minutes dated 24 July 2019 for [redacted] did not reference two surveillance data reports from rheumatoid arthritis registries (Swedish Biologics register (ARTIS) and Spanish Registry of Biologics in Rheumatology (BIOBADASER)) that were available at the time of the meeting. Lilly confirmed in writing that these interim study reports had been reviewed by the SST, but the review had erroneously not been documented in the minutes. The SST minutes were the official record that demonstrated that all available data had been reviewed for signal detection purposes; no other record was made.
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]

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

MI.2 Oversight of third-party service providers

Finding MI.2 a)

No Initial Compliance Check Visit (ICCV) was conducted for one of the three study sites sampled during the inspection for studies [redacted] For these studies, Lilly used the patient registries [redacted] and [redacted] respectively, which were managed by the third-party Corrona.

The Corrona Registry Monitoring Plan (version date: 31 January 2019) stated that centralised (remote) monitoring activities would include an ICCV, where the first three enrolment visits at a site would be reviewed in detail. The sites were required to submit scanned copies of the subject enrolment questionnaires and a data quality review was undertaken by Corrona to verify that the site followed all required data collection procedures and the subject case history was clinically logical.

For site 217 [redacted] registry), it was identified that Corrona had requested and received the ICCV scans; however, these had not been sent to the Corrona study monitor, as expected, in order to complete the data quality review. Nevertheless, site 217 was approved to enrol on 16 September 2019 and had 63 active subjects at the time of the inspection.

The [redacted] study protocol (version 1.0, 31 October 2017) stated *"Corrona or its designee monitors the conduct of the registry at each investigative site. Monitoring is primarily conducted remotely."* The associated Corrona Rheumatoid Arthritis (RA) Drug Safety & Effectiveness Registry protocol (version 15.0, 01 May 2019) stated *"At regular intervals as defined by the registry monitoring plan, Investigative sites are contacted by Corrona representatives to participate in remote and onsite monitoring visits."*

Post-inspection request: The response to this inspection finding should include the results of an assessment of the extent of this issue for these studies for the ICCV, as well as an assessment of the adherence to the schedule for the Interim Compliance Check Visit – [redacted]

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[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)

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[redacted]

Finding MI.2 b)
Lloyds Pharmacy Clinical Homecare (LPCH) was contracted as a PSP service provider by Lilly for multiple PSPs, including two UK [redacted] PSPs that were reviewed during the inspection: • LPCH standard [redacted] (initiated in August 2019) • [redacted] (in conjunction with Quintiles, initiated in October 2016 and terminated in April 2020) In April 2018, sample checks were introduced whereby the LPCH pharmacovigilance team submitted a listing of all interactions from the customer relationship management database for five requested days each quarter, in order for Lilly to complete a sample check of the interactions to ensure all AE/PCs had been identified and reported. The requirement to complete this activity was detailed in the Quality Agreement (last revised 29 January 2020, version 6.0). On request of evidence of this activity during the inspection, it was identified that interactions concerning [redacted] had not been included within the sample check data for the following months: • June 2018 • August 2018 - January 2019 • April 2019 - September 2019 It was acknowledged that LPCH managed a number of PSPs for other Lilly products, for which listings of interactions had been provided for the above time periods and the sample check had been completed.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

MI.3 Pharmacovigilance system master file

Finding MI.3 a)

Annex G 'Quality System' of the PSMF (version 33, 18 June 2020) did not include details of six audits conducted between July and September 2019:

- [redacted] Audit of [redacted] (PSP third party), 07 - 08 July 2019
- [redacted] Audit of [redacted] (PSP third party), 12 -15 July 2019
- [redacted] Audit of [redacted] PSP third party), 17 - 18 July 2019
- [redacted] Audit of [redacted] (PSP third party), 26 August 2019
- [redacted] Audit of [redacted] 17 -19 September 2019
- [redacted] Audit of [redacted] (PSP third party), 26 September 2019

As per GVP II.B.4.8., "*An annex to the PSMF shall contain the following documents […] A list of all completed audits, for a period of five years*".

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]	

MI.4 Collection of adverse events

Finding MI.4 a)
There was a discrepancy between the protocol for baricitinib study [redacted] (version 1.0, 31 October 2017) and Lilly procedural document 'Adverse Event Collection and Reporting in Observational Studies' [redacted] version 6.0, 10 December 2018) in relation to the timeline for reporting protocol-defined serious adverse events (SAEs) to Lilly. The protocol for the baricitinib study stated that protocol-defined SAEs would be reported to Lilly within 72 hours of Corrona awareness. This timeframe was also specified in the Lilly_Corrona Subscription Agreement (12 April 2019), which provided the contractual basis for Lilly's access to the Corrona Rheumatoid Arthritis Registry for the purpose of undertaking this study (Exhibit A, section B (Safety Reporting & Pharmacovigilance)), as well as in the Drug Safety Reporting Plan (last revised 22 November 2019). Although SAEs were being reported within 72 hours, Lilly procedural document 'Adverse Event Collection and Reporting in Observational Studies' stated that, for primary data collection studies, all protocol-defined SAE(s) should be reported to GPS local affiliate/GPS CM within 24 hours.
Root Cause Analysis
[redacted]

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

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

Preventative Action(s)
[redacted]

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

C.4.4 Comments

- Attachment B (Targeted Adverse Events) to the Lilly_Corrona Subscription Agreement (12 April 2019) did not include the COVID-19 related terms that were included in the Targeted Adverse Event List in Corrona Rheumatoid Arthritis (RA) Drug Safety & Effectiveness Registry Protocol [redacted] version 15.0) Appendix B (version 1.1, 27 May 2020). Lilly should consider how timely updates to the list of Targeted Adverse Events in the Lilly_Corrona Subscription Agreement are implemented.

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 Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

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).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- EMEA/CHMP/313666/2005: "Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 6/24884-0006	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Eli Lilly	**DATES**	22 - 23 June 2020 06 - 07 July 2020
LOCATION	Remote inspection	**START TIME**	09:00am on all days

Inspection plan (N.B. the plan may be subject to change in the lead-up to, or during, the inspection)

The scope of the inspection will include the following topics:

- **Collection and collation of adverse drug reactions (ADRs)**
  - To include post-authorisation safety studies (PASS) and patient support programmes (PSP)
- **Management and reporting of ADRs**
  - To include data entry and case assessments, submission to EudraVigilance, and follow-up activities
- **Signal management**
  - To include signal detection and evaluation activities, actioning of signals and quality requirements
- **Periodic safety update reports (PSURs)**
  - To include data accuracy and completeness

Review of the above topics will primarily focus on two products: baricitinib (Olumiant) and ixekizumab (Taltz).

Monday 22 June 2020 (day 1):

An opening meeting will be held at the start of the inspection *(19 June 2020)* by teleconference (TC), which will be led by the lead inspector. The agenda will be as follows:

- Review of the scope and inspection plan
- Company presentation by Eli Lilly to provide an overview of the company, pharmacovigilance system and quality system. The presentation should last no longer than 20 minutes.

The remainder of the inspection will consist of remote document review. Interview sessions with company personnel are not intended. However, please provide a designated contact point who can assist with any ad hoc questions from the inspectors or arrange calls between inspectors and subject matter experts if required.

Tuesday 23 June 2020 (day 2)

Remote document review and ad hoc queries from inspectors where necessary.

Monday 06 July 2020 (day 3)

Remote document review and ad hoc queries from inspectors where necessary.

Tuesday 07 July 2020 (day 4)

Remote document review and ad hoc queries from inspectors where necessary.

A closing meeting will be held via TC on ~~day 4~~ *08 July 2020* (timing to be confirmed) during which feedback on the inspection will be provided to the company.

Eli Lilly are requested to complete the below with the names and job titles of the designated contact point and those staff who will be dialling in to the opening meeting.

Designated contact point:

[redacted]

Opening meeting attendees:

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[redacted]