Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: G.L. Pharma

MHRA Inspection Number: Insp GPvP 42504/16698876-0001

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CCSI	Company Core Safety Information
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAH	Marketing Authorisation Holder
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QP	Qualified Person
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	G.L. Pharma, [redacted]
Site(s) of inspection:	G.L. Pharma, Leopold-Bartenstein-Strasse. 1, A-8502 Lannach, Austria
Main site contact:	[redacted] G.L. Pharma GmbH, Leopold-Bartenstein-Strasse. 1 A-8502 Lannach, Austria [redacted]
Date(s) of inspection:	25 – 27 November 2019 (onsite inspection)
Lead Inspector: **Accompanying Inspector(s):**	[redacted]
Previous inspection date(s):	N/A
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Name and location of EU QPPV:	[redacted] G.L. Pharma GmbH, Leopold-Bartenstein-Strasse. 1 A-8502 Lannach, Austria [redacted]
Global PV database (in use at the time of the inspection):	BPI-Pheda (bespoke database hosted by service provider Heacon Service GmbH)
Key service provider(s):	Global safety database hosted by Heacon Service GmbH (formerly BPI Service GmbH), who also provided services in ICSR processing, signal detection activities and literature screening. Preparation of PSURs and RMPs (on an ad-hoc basis) and pharmacovigilance audits provided by DREHM Pharma GmbH.
Inspection finding summary:	03 Major findings 02 Minor findings
Date of first issue of report to MAH:	08 January 2020
Deadline for submission of responses by MAH:	12 February 2020
Date(s) of receipt of responses from MAH:	12 February 2020 05 March 2020
Date of final version of report:	06 March 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

G.L. Pharma 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.

G.L. Pharma is an Austrian-based international pharmaceutical company that markets generic products globally via branch offices and licence partners. The company was formed in 2009 following a merger between Lannacher Heilmittel GmbH and Gerot Pharmazeutika GmbH. In the UK, G.L. Pharma has 52 marketing authorisations licensed through national, decentralised and mutual recognition procedures. Generic products marketed in the UK included [redacted] At the time of the inspection, significant pharmacovigilance activities were outsourced to two companies; Heacon Service GmbH (formerly BPI Service GmbH) who hosted the global safety database and provided services in ICSR processing, signal detection activities and literature screening, and DREHM Pharma GmbH who provided services in PSUR and RMP preparation and pharmacovigilance audits.

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B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at G.L. Pharma's offices in Lannach, Austria. Personnel from G.L. Pharma attended the Lannach site in order to participate in the inspection.

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).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 05 July 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. The detail of these requests is 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. The inspection included a scheduled office-based inspection day; however, this was not required, and the inspection finished one day earlier than planned.

A closing meeting was held to review the inspection findings at G.L. Pharma, Lannach, on 27 November 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.

SECTION C: INSPECTION FINDINGS

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

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

C.2 Definitions of inspection finding gradings

Critical (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 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, Regulations 76

Eudralex Volume 2A, Chapter 5
Section 2.1.1. Submission of Type IA variations *"Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder"*.

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 the Patient Information Leaflet (PIL), in order that healthcare professionals and patients are able to use the medicinal product correctly on the basis of full and comprehensive information.

The following findings were identified in relation to control and maintenance of product safety information:

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Finding MA.1 a)
Two batches of [redacted] were certified for release by the Qualified Person with an out of date PIL that had been superseded more than six months prior by a version with updated safety information. A [redacted] variation was submitted on 20 December 2018 to add 'diplopia' to section 4.8 of the SmPC and 'double vision' to section 4 of the PIL following a PSUR single assessment

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procedure [redacted]

One batch [redacted] CR prolonged release tablets [redacted] was certified on 23 August 2019, eight months after the [redacted] variation submission, and one batch [redacted] CR prolonged release tablets [redacted] was certified on 26 June 2019, six months and six days following [redacted] variation submission.

Published MHRA guidance states that [redacted] variations are classed 'do-and-tell', and the MHRA should be notified of the change within two weeks of implementation by the MAH: https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation It is therefore the expectation of the MHRA that batches with the old PIL are not released over six months after [redacted] variation submission.

Details of the affected batches have been reviewed by the MHRA's Defective Medicines Reporting Centre (DMRC) and no further action was considered necessary.

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]	

Finding MA.1 b)

Safety variations were submitted outside of acceptable timeframes, and there were no defined timeframes for the submission of safety variations documented in any SOP or working instruction.

i) Variations to product information following CCSI changes:

The CCSI [redacted] was updated on 28 February 2018, and included the addition of a new contraindication regarding use in patients with known urea cycle disorders to section 4.3 of the SmPC, and the addition of warnings to section 4.4, including aggravated convulsions, use in patients with carnitine-palmitoyl transferase (CPT-)II deficiency and concomitant consumption of alcohol. However, there were significant delays in submitting variations to update the product information with this new information for [redacted] CR:

a. A [redacted] variation to update [redacted] was submitted on 13 November 2019, over 20 months following CCSI update.
b. A [redacted] variation to update [redacted] prolonged-release tablets [redacted] was submitted on 27 August 2019, almost 18 months following CCSI update.

ii) Variations to product information following CMDh guidance:

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] After this was published, three G.L. Pharma [redacted] were launched in the UK:

- [redacted] solution for [redacted] was marketed in the UK on 19 June 2018
- [redacted] was marketed in the UK on 15 February 2019
- [redacted] was marketed in the UK on 15 February 2019

However, a grouped [redacted] variation to update the product information with this warning for all three products was not submitted until 18 March 2019, nine months after the solution for injection or infusion product was marketed, one month after the oral solution products were marketed, and 13 months after the

advice was published.

If a deadline for variation submission has not been specified, variations should be submitted within six months of identification to ensure that the product information is kept up to date with current scientific knowledge. For non-marketed products, processes should be in place to ensure that the product information is up to date at launch.

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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)

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[redacted]

Finding MA.1 c)
Comparisons between the product information of G.L. Pharma products and their reference products were not being conducted routinely to identify relevant safety updates. [redacted] of a draft SOP for reference safety information maintenance [redacted] November 2019] stated that the CCSI may be updated as a result of safety updates in the originator text. However, it was confirmed verbally during the inspection that comparisons with the reference product were not being conducted routinely, only following updates of the product information from other routes (i.e. PRAC recommendations). This finding is minor in nature as no impact was observed from the sample reviewed during the inspection. It has however been grouped as part of this major finding and a full impact assessment should be completed as part of the CAPA.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)

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[redacted]

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

MA.2 Pharmacovigilance audit

Requirements:

Directive 2001/83/EC as amended,
Article 104(2) *"The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system […]"*

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

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

GVP Module IV – Pharmacovigilance audits (Rev 1)
IV.B.1. *"Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.*
In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes."
IV.B.1. (footnote 3) *"Benchmarking, reviews of qualifications, risk assessment questionnaires, surveys or other activities in which evidence of fulfilment of pharmacovigilance requirements is not independently obtained and evaluated, would not be regarded as an audit."*

Finding MA.2 a)
G.L. Pharma had not conducted any pharmacovigilance audits of its affiliates or third parties. In August 2017, a risk assessment was conducted for all partners to assign a risk score and prioritise partners for pharmacovigilance audit. Following this, audit questionnaires were sent to all country affiliates in September 2017, excluding Germany who did not have an independent office from the Austrian headquarter office, as well as four third parties in September 2017 and a further eight third parties in December 2018. The questionnaires did not require the submission of evidence to support fulfilment of pharmacovigilance requirements, and hence are not regarded as an audit. To note, approximately 30 third parties, including distributors, licensing partners and service providers, were included in the initial risk assessment. No further risk assessment has been conducted and at the time of the inspection there were 45 third parties listed in PSMF Annex C ([redacted] 14 November 2019).
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

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MA.3 Pharmacovigilance agreements

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 11(2) *"Where a marketing authorisation holder has subcontracted some of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks."*

GVP Module I – Pharmacovigilance systems and their quality systems
I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorisation holder *"Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. When preparing contractual arrangements, the marketing authorisation holder should include sufficiently detailed descriptions of the delegated tasks, the related interactions and data exchange, together with, for example, agreed definitions, tools, assignments and timelines."*

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)
VI.B.7. Submission of individual case safety reports *"Where the marketing authorisation holder has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the marketing authorisation holder and the person/organisation to ensure that the marketing authorisation holder can comply with the submission of valid ICSRs within the appropriate time frames. These procedures should in particular specify the processes for the exchange of safety information, including the timelines and responsibilities for the regulatory submission of valid ICSRs. They should be organised in order to avoid the submission of duplicate ICSRs to the competent authorities."*

An MAH may subcontract certain activities of the pharmacovigilance system to third parties. The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the MAH.

The following finding was identified in relation to pharmacovigilance agreements:

Finding MA.3 a)

Two examples were identified of distributors in territories with no G.L. Pharma presence that did not have agreements for the exchange of safety reports or reassurance they had received all safety information.

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i) There was no agreement for the exchange of pharmacovigilance relevant information with B.P. Pharma, who act as the agent for G.L. Pharma in Egypt, distributing [redacted] [redacted] The 'Agency Agreement' with B.P. Pharma was entered into on 01 August 1995. Evidence was seen by inspectors of efforts made between 11 March 2016 and 05 May 2017 to establish a pharmacovigilance agreement. However, since May 2017, no further efforts had been made, and at the time of the inspection no pharmacovigilance agreement had been signed to ensure the sending of relevant safety reports from B.P. Pharma to G.L. Pharma.

ii) There was a delay in over three years in establishing a pharmacovigilance

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agreement with Kent Pharmaceuticals Ltd. who are contracted as a distributor in UK for [redacted] products. The first distribution agreement with Kent Pharmaceuticals Ltd. was dated 08 July 2016; however, a pharmacovigilance agreement with Kent Pharmaceuticals Ltd. was not signed until 21 November 2019, four days prior to the start of the MHRA inspection. The agreement defined the pharmacovigilance responsibilities for these products, including the exchange of pharmacovigilance relevant information from Kent Pharmaceuticals Ltd. to G.L. Pharma, and a three-monthly reconciliation. At the time of the inspection, there were no plans to conduct a reconciliation with Kent Pharmaceuticals Ltd. to ensure that all notifications of safety reports had been received prior to the signing of the pharmacovigilance agreement.

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]	

C.4.3 Minor findings

MI.1 Written procedures

Finding MI.1 a)
UK PILs for [redacted] products and the UK PIL and SmPC for G.L. Pharma's [redacted] product were published by the UK distributor Healthcare Pharma Ltd. (formerly Chanelle Medical U.K. Ltd.) on the UK electronic Medicines Compendium (eMC) website, together with telephone and email contact details for medical information at Healthcare Pharma. Although there was a pharmacovigilance agreement in place with Healthcare Pharma Ltd.*, neither G.L. Pharma or Healthcare Pharma had any written procedures to support the maintenance of this information on the eMC website or the management of adverse event (AE) reports received via the Healthcare Pharma medical information contact details published on the eMC website. Collection of individual case safety reports from any source and the update of product information in light of scientific knowledge are critical pharmacovigilance processes that require specific quality system procedures. To note, the product information published on the eMC website was not out of date (no relevant safety variations had been submitted/implemented for these products since Healthcare Pharma Ltd. first published the PILs online). *A transfer agreement dated 22 November 2019 following the organisation's change of name, original pharmacovigilance agreement with Chanelle Medical UK Ltd. dated 23 June 2014.
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]

[redacted]	

Finding MI.1 b)

In relation to the documentation of processes involved in the maintenance of product safety information, there was no SOP or working instruction that defined timelines for the implementation of updated PILs into packs.

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]	

MI.2 Periodic Safety Update Reports (PSURs)

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Finding MI.2 a)

One example of incorrect case type categorisation was identified in PSUR tables:

Spontaneous adverse event (AE) case [redacted] containing a serious AE of "Toxicity to various agents" was categorised inconsistently in two tables in the [redacted] (DLP 13 April 2013 to 12 April 2018). In Appendix 2, the AE case was included in data for 'Spontaneous, including competent authorities (worldwide) and literature' in the table "*Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from Post-Marketing Data Sources*". However, in the table "*Cumulative and Interval Summary Tabulations of Fatal Cases from Post-Marketing Data Sources*", which was supposed to be a subset of the cases in the aforementioned table, the events were included incorrectly in data for 'Non-interventional post-marketing study and reports from other solicited sources'.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

C.4.4 Comments

1. Pharmacovigilance agreements:
It was confirmed that written procedure [redacted] 'Verträge in der Pharmakovigilanz' [PV Agreements] (effective 11 November 2019, unchanged from [redacted] effective 04 May 2018) states that negotiations are started with a third party if there is a necessity to create a pharmacovigilance agreement, once there is at least a non-disclosure agreement in place and a letter of intent with the third party.

However, there were no corresponding written procedures in the licensing team or international marketing team to notify the pharmacovigilance department when planning to establish a new partnership with another organisation. The MAH should consider either including a requirement in the written procedures to contact the pharmacovigilance department or have members of the relevant teams trained on the pharmacovigilance written procedure.

2. Management of deviations:
A deviation concerning safety variations submitted one day late to the Austrian National Competent Authority was incorrectly not added to the deviation tracker.

The late submissions were initially identified and raised to the QPPV on the day the variations were due to be submitted (10 October 2018). Documented evidence showed that the QPPV had further investigated the root cause and considered whether further action was required for this non-compliance when compiling the key performance indicators (KPIs) for Annex F in March 2019.

However, the deviation was not logged on the Deviation Tracker in accordance with section 6.6 of [redacted] 'Abweichungen im Bereich Pharmakovigilanz' [Deviations (PV)] (effective 02 January 2018, superseded on 11 November 2019, with no change to this section).

The safety variations were submitted following a PSUR single assessment procedure for [redacted] and concerned G.L. Pharma [redacted] and [redacted] products licensed in Austria.

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.

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.

APPENDIX I REFERENCE TEXTS

- 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).
- Eudralex Volume 2A, Chapter 5: Guidelines of 16 May 2013 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 - C (2013) 2804.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 42504/16698876-0001	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	G.L. Pharma	**DATE**	25 November 2019
LOCATION	G.L. Pharma GmbH, Leopold-Bartenstein-Strasse 1, 8502 Lannach, Austria	**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 and the quality system *(approx. 20 minutes)*	[redacted]	All welcome
Receipt and review of documentation		Inspectors only
Spontaneous sources of safety data To include: • Pharmacovigilance agreements and safety data exchange with third parties • Medical information and product quality complaints	[redacted]	[redacted]
LUNCH	-	-

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Maintenance of reference safety information • Identification of required updates from all sources • Submission of safety variations • Implementation of approved updates to product information	[redacted]	[redacted]
Data management To include: • Migration of legacy data	[redacted]	

MHRA INSPECTION NUMBER	Insp GPvP 42504/16698876-0001	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	G.L. Pharma	**DATE**	26 November 2019
LOCATION	G.L. Pharma GmbH, Leopold-Bartenstein-Strasse 1, 8502 Lannach, Austria	**START TIME**	09:00am
Purpose of Interview	**Session Lead**	**Staff to be interviewed**	
Document Review	-	Inspectors only	
Quality assurance and oversight of the pharmacovigilance system To include: • Pharmacovigilance audit • Deviation management • Maintenance of the PSMF	[redacted]	[redacted]	
LUNCH	-	-	

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Periodic safety update reports	[redacted]	[redacted]
Risk management activities • Additional pharmacovigilance activities and additional risk minimisation activities associated with valproate	[redacted]	[redacted]
Document Review	-	Inspectors only

MHRA INSPECTION NUMBER	Insp GPvP 42504/16698876-0001	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	G.L. Pharma	**DATE**	27 November 2019
LOCATION	G.L. Pharma GmbH, Leopold-Bartenstein-Strasse 1, 8502 Lannach, Austria	**START TIME**	09:00am

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Ad-hoc questions and queries	-	-
Document review	-	Inspectors only
LUNCH	-	-
Ad-hoc questions and queries	-	-
Document review	-	Inspectors only
~~Interim~~ Closing meeting	[redacted]	All welcome