Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Gedeon Richter Plc

MHRA Inspection Number: Insp GPvP 4854/25239-0004

10 South Colonnade, Canary Wharf, London E14 4PU **T** 020 3080 6000 **E** gpvpinspectors@mhra.gov.uk
www.gov.uk/mhra

Table of Contents

ABBREVIATIONS

ADR	Adverse Drug Reaction
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
LPCH	Lloyds Pharmacy Clinical Homecare
LSO	Local Safety Officer
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PAQC	Post Approval Quality Check
PBRER	Periodic Benefit Risk Evaluation Report
PSMF	Pharmacovigilance System Master File
PSP	Patient Support Programme
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
SOP	Standard Operating Procedure
UK	United Kingdom
US	United States of America

SECTION A: INSPECTION REPORT SUMMARY

Section 40 & 43

Inspection type:	Statutory National Inspection
System(s) inspected:	Gedeon Richter, [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted] Address: Gedeon Richter Plc., Gyömrői út 19-21, Budapest 1103, Hungary [redacted]
Date(s) of inspection:	19 – 22 October 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	08 – 11 December 2014 15 – 18 May 2013 26 – 27 November 2008 24 – 26 October 2007
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	The inspection primarily focused on two centrally authorised products: [redacted]
Name and location of EU QPPV:	[redacted] Address: Gedeon Richter Plc., Gyömrői út 19-21, Budapest 1103, Hungary [redacted]
Global PV database (in use at the time of the inspection):	ARISg LifeSphere Safety MultiVigilance (LSSMV) (commercially available)
Key service provider(s):	BioClinica LLC acted as a global case processing site for the majority of products in the portfolio. Global Drug Safety Services at [redacted] acted as the global case processing site for the remaining products. [redacted] provided local pharmacovigilance services in the UK, including medical information services.
Inspection finding summary:	4 Major findings 3 Minor findings
Date of first issue of report to MAH:	20 November 2020
Deadline for submission of responses by MAH:	13 January 2021 Updated responses due 28 January 2021
Date(s) of receipt of responses from MAH:	13 January 2021 Updated responses received 28 January 2021
Date of final version of report:	29 January 2021
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Gedeon Richter 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.

Gedeon Richter Plc. is a global pharmaceutical company, headquartered in Budapest, Hungary. This is also the location of the Global Pharmacovigilance Department, the EU QPPV and the PSMF. Gedeon Richter UK Ltd., the UK affiliate, outsourced local pharmacovigilance services to Diamond PV Services Ltd.

The company product portfolio comprised a range of original and generic products licensed via centralised and national procedures, with the primary focus on central nervous system and women's healthcare therapeutic areas.

This inspection focused primarily on two centrally authorised products, both subject to additional monitoring:

Section 43

- [redacted] an antipsychotic medicine authorised on 13 July 2017 for the treatment of schizophrenia in adults.
- [redacted] a biosimilar medicine authorised on 04 January 2017 for the treatment of osteoporosis.

BioClinica LLC acted as a global case processing site for the majority of products in Gedeon Richter's portfolio, including [redacted]

B.2 Scope of the inspection

The inspection included a review of specified global and local pharmacovigilance processes, focusing primarily on two centrally authorised products: [redacted]

Due to the Covid-19 pandemic, 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 and listings of medical information enquiries and product complaints). 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 and the quality management system were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

Section 43

B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] 29 June 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.

A closing meeting was held via teleconference to review the inspection findings on 22 October 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

At the time of the inspection, the pharmacovigilance system was undergoing numerous developments. This included significant revision and redesign of the signal management processes. Changes included a new algorithm for statistical signal detection (implementation planned for April 2021) and the introduction of a risk-based approach for signal detection from the scientific literature. Additionally, there was an ongoing QMS project to implement TrackWise software.

Section 43

Further changes to the pharmacovigilance system that the company had made since the previous inspection in December 2014 included a change of EU QPPV in January 2018 to [redacted], and implementation of an enhanced PSMF structure, which was completed in June 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

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 Quality management system

Requirements:

GVP Module III – Pharmacovigilance inspections (Rev 1)
III.C.5. Role of marketing authorisation holders and applicants
"Marketing authorisation holders with authorised products and applicants who have submitted new applications under the centralised procedure are subject to pharmacovigilance inspections (see III.B.1.). Therefore both have responsibilities in relation to inspections, including but not limited to the following: […]

- *to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings."*

Finding MA.1 a)

There was a failure to remediate non-compliance identified through two previous pharmacovigilance inspections of Gedeon Richter.

A major finding in the area of signal management was issued during an MHRA inspection conducted in 2013, as it was identified that there was no cumulative review of serious expected and non-serious cases, other than at the time of PSUR production. A subsequent re-inspection conducted in 2014 by the MHRA found there had been limited progress made to address these deficiencies, and a repeat major finding was issued as cumulative review of ICSR data continued to be limited to serious unlisted cases.

Following these inspections, Gedeon Richter introduced a new signal detection process in February 2016, in which a monthly statistical signal detection process was conducted for all products within the portfolio. However, the quantitative method was based on a comparison of the frequency of adverse reactions in the last month with the previous 12 months on a rolling basis, and hence did not assess cumulative data.

An additional signal detection process was initiated in July 2019, in which weekly alerts were produced for high-risk products. As part of these weekly alerts, MedDRA PTs of serious approved cases received in the week prior were presented, along with their cumulative totals. However, this review was not inclusive of non-serious cases and was limited to products classified as high-risk.

As such, the non-compliance in signal detection methodology, which was initially identified seven years ago via pharmacovigilance inspections, remained unresolved.

This finding has been graded as major as Gedeon Richter self-identified the need to initiate a project to review and revise the signal detection process. As part of the ongoing project, cumulative data will be incorporated within the statistical signal detection methodology, with a planned implementation date of April 2021.

Section 43

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

Section 43

[redacted]

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

MA.2 Periodic safety update reports

Requirements:

GVP Module VII – Periodic safety update report (Rev 1)
VII.B.5.6.2. PSUR sub-section "Cumulative summary tabulations of serious adverse events from clinical trials"
"The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable."

VII.B.5.6.3. PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"
"Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table […]."

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.1.2. Solicited reports
"*They [solicited reports] should have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria (see VI.B.2. for ICSRs validation).*"

Periodic safety update reports (PSURs) provide an analysis of the current understanding of a product. As part of this inspection, the [redacted] PSUR covering the period 06 April 2019 – 05 October 2019 was reviewed in detail.

The following findings were noted in relation to the data held within the summary tabulations of the PSUR:

Finding MA.2 a)
Adverse events from solicited post-marketing cases that had been assessed by the company

as unrelated and for which no reporter causality had been provided, were automatically and incorrectly included in the PSUR table in Appendix 2.2 'Summary Tabulation of Serious and Non-serious Adverse Drug Reactions from Post-Marketing Data Sources' [emphasis added].

Any events that have been appropriately assessed by the company as unrelated to the company product, and for which no contradictory information has been received from the reporter, should not be classified as suspected adverse reactions. As such, these events should be excluded from the summary tabulation of post-marketing adverse drug reactions in the PSUR. It should be noted that 20% of all [redacted] cases in the global safety database originated from US post-marketing surveillance studies.

Section 43

As an example, the serious event of 'bedridden', from solicited case [redacted] received in the PSUR interval for [redacted] without a reporter causality, was assessed by the company as 'not related'; however, the event had been incorrectly included in the summary tabulation of the [redacted] PSUR (DLP 05 October 2019).

Post-inspection request: The MAH should highlight to assessors the discrepancies in the event numbers as a result of this finding, along with the corrected event numbers, in the relevant sections of subsequent PSURs.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)
[redacted]

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

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

Finding MA.2 b)

Serious adverse events were presented with blinded study drug in Appendix 2.1. 'Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials' of the [redacted] PSUR (DLP 05 October 2019), despite originating from completed studies that had undergone end-of-study unblinding. The examples identified were as follows:

Case ID	Event PT	Clinical Trial	Date of final code-breaking
[redacted]	Fall	[redacted]	17 March 2014
[redacted]	Social stay hospitalisation	[redacted]	08 January 2015
[redacted]	Iron deficiency anaemia	[redacted]	Regulatory code-breaking: 31 October 2016 Final code-breaking: 13 December 2017
[redacted]	Physical assault	[redacted]	23 March 2018

Information in the safety database had not been updated with unblinding data, and hence at the time of the inspection, it was not known whether the events occurred with [redacted] placebo or comparator treatment.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

Preventative Action(s)

[redacted]

Section 43

[redacted]

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

MA.3 Signal management for biological medicines

Requirements:

GVP Product- or population-specific considerations II: Biological medicinal products
P.II.B.4. Signal Management
"Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological and important differences between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change). […]

"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). […]

"Any signal should be evaluated in the context of batch-specific exposure data, including numbers/codes of delivered or sold batches, their size and the regions or countries where the respective batches have been delivered."

GVP Module IX – Signal management (Rev 1)
IX.B.5. Quality requirements
"Any signal management system should be clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardised, that these tasks are conducted by staff with appropriate qualifications and

expertise and that there are provisions for appropriate control and, when needed, improvement of the system."

GVP Product- or population-specific considerations II: Biological medicinal products (GVP P.II) became effective on 16 August 2016 to address several specific challenges in pharmacovigilance that are associated with biological medicinal products.

Section 43

Gedeon Richter's product portfolio in the UK included two biological medicinal products, one of which was [redacted] a biosimilar medicinal product indicated for the treatment of osteoporosis.

The following findings were identified in relation to signal management for biological products:

Finding MA.3 a)

Gedeon Richter's signal management processes for biological medicinal products failed to account for the requirements outlined in GVP P.II. The following deficiencies were identified:

- There were no processes in place to detect any acute and serious new risks that may emerge following a change in the quality of a biological, whether that originated from differences between batches of the same product or unanticipated changes in the manufacturing process. It is acknowledged that scheduled changes in the manufacturing process were notified to pharmacovigilance, although this process was not formally documented (please refer to finding MA.3 b).

- Denominator data and data of suspected adverse reactions were not analysed to support continuous signal detection or the identification of any apparent changes in adverse drug reaction (ADR) reporting rates or trends that could indicate new signals.

- There were no processes in place to ensure signals for biological products were evaluated in the context of batch-specific exposure data [emphasis added]. For example, the signal evaluation report for teriparatide and pancreatitis (signal ID, [redacted]; dated 06 July 2020) discussed cumulative patient exposure by region but did not review batch-specific exposure data.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

Finding MA.3 b)
There was no written procedure describing the process of informing pharmacovigilance of changes to the manufacturing process of biological medicinal products, and the subsequent actions taken to consider the impact on signal detection. Prior to implementing any changes in the manufacturing process of a biological medicinal product, a comparability exercise was conducted; the result of which was shared with relevant personnel in the pharmacovigilance team through a safety evaluation document. During the inspection, evidence was provided of this process in practice; however, the process was not formalised in a written procedure. This is a minor finding relating to the quality requirements for signal management; however, it has been grouped with the major finding regarding signal management for biological medicines.
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

Section 43

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

MA.4 Management of adverse events and adverse drug reactions

Requirements:

Directive 2001/83/EC as amended
Article 107(3) "*Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the 'Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.*"

Commission Implementing Regulation (EU) No. 520/2012
Article 2 "*The pharmacovigilance system master file shall contain at least all of the following elements […]*
(5)(c) a description of the system for monitoring the performance of the pharmacovigilance system and for the compliance with Article 11"

Article 11(1) "*Specific quality system procedures and processes shall be in place in order to ensure the following […]*
(c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the Eudravigilance database […]"

GVP Module I – Pharmacovigilance systems and their quality systems
I.C.1.1. Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the EU
"*Compliance information should be provided to the QPPV on a periodic basis.*"

I.C.1.3. Role of the qualified person responsible for pharmacovigilance in the EU
"In relation to medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV should include: […]

- *ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the competent authorities in Members States and the Agency*"

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.2. Validation of report
"Four minimum criteria are required for ICSRs validation: […]

"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 […]"

Individual case safety reports (ICSRs) are used to facilitate electronic reporting requirements of suspected ADRs to the EudraVigilance database. ICSRs are important sources of safety information, used in signal detection to assess the benefit-risk balance of medicinal products. It is possible that a single ICSR could generate a signal with new safety information that changes the benefit-risk balance of a product, and ultimately impacts on patient safety. It is therefore very important that the information presented in ICSRs is accurate and complete to enable scientific evaluation of the case.

Marketing authorisation holders (MAHs) are required to have a quality management system in place to ensure compliance to the necessary quality standards. The EU QPPV should have oversight of this system and is ultimately responsible for ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to competent authorities, including the submission of serious and non-serious adverse reactions to the EudraVigilance database.

Deficiencies were identified with regards to Gedeon Richter's quality management system and EU QPPV oversight of ICSR quality. Additionally, based on the sample of cases reviewed during the inspection, a number of errors in case processing were identified that resulted in the submission of inaccurate information to the EudraVigilance database.

It is expected that Gedeon Richter shares the following findings with the relevant case processing service provider, and where applicable, a joint response to the inspection findings should be provided.

The following findings were identified:

Section 43

Finding MA.4 a)

The EU QPPV had no oversight of ICSR quality.

In September 2019, due to a lack of resource, a planned exception was raised to reduce the sample size of ICSRs checked during the weekly Post-Approval Quality Check (PAQC) process. The sample size was defined as 10% in [redacted] 'Post-Approval Quality Check (PAQC) for Post Marketing Individual Case Safety Reports at Richter Group [redacted] 22 April 2020); the exception was to check only five cases each week, which was approximately 2% of cases received each week. Due to the small sample size, the monthly analysis of the outcomes of ICSR quality checks was also halted.

The PAQC process was reinstated from 01 August 2020; however, no metrics on ICSR quality were presented in the current version of the PSMF [redacted] 14 October 2020) and no metrics had been presented to the QPPV for at least one year.

Section 43

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

Section 43

Deliverable(s)	Due Date(s)

Finding MA.4 b)

Examples of serious adverse reactions were identified that had incorrectly not been submitted to the EudraVigilance database:

i. Spontaneous UK case for received on 22 May 2020, described a patient who was hospitalised with dyspnoea (serious due to hospitalisation), had a lower respiratory tract infection (non-serious) and a skin ulcer (non-serious). Whilst processing the case, the reaction term of dyspnoea was, in error, manually changed to being reported as an event for 'sister' instead of 'patient', which resulted in the case being submitted to EudraVigilance as a non-serious case, omitting the serious adverse reaction of dyspnoea.

ii. (0): Spontaneous US case for received on 15 July 2019, described a suspected adverse reaction of anuria and stated that the "*patient did not urinate for two days*". This case was incorrectly assessed as non-serious by the medical reviewer and was therefore not reported to EudraVigilance. Anuria was included on the EMA Important Medical Event terms list (MedDRA version 21.1, 17 September 2018), which was used by Gedeon Richter to assign event seriousness.

iii. (1): Spontaneous US case for received on 23 September 2019, described a patient who underwent an induced abortion following maternal exposure during pregnancy and experienced multiple serious complications following the termination. The case was linked to US case for the foetus, which described the event of spina bifida. Both cases were correctly submitted to EudraVigilance; however, the event of induced abortion was not correctly coded as a suspected adverse reaction in the parent case.

Root Cause Analysis

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Section 43

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

Section 43

[redacted]

Finding MA.4 c)

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

i. [redacted] Spontaneous UK case for [redacted] received on 24 July 2020 and submitted to EudraVigilance on 29 July 2020, reporting the MedDRA PT of 'Hospitalisation' only. Consent to follow-up the report was denied by the reporter.

ii. [redacted] (0): Post-marketing solicited US case for [redacted] received on 30 July 2019 and reported to EudraVigilance on 06 August 2019, reporting the MedDRA PTs of 'Death' and 'Adverse event' only. Follow-up had been requested but no further information on the events was received.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

Preventative Action(s)
[redacted]

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

Finding MA.4 d)
Multiple examples of errors in the listedness assessment of adverse events were identified. Examples included: i. [redacted] (0): Serious post-marketing solicited case for [redacted] received from Spain on 08 June 2020, included the event arrhythmia that was incorrectly assessed as listed (labelled per the CCDS). Arrhythmia was not listed in the [redacted] CCDS [redacted] dated 23 February 2018 and [redacted] dated 19 October 2020). ii. [redacted] (0): Non-serious spontaneous UK case for [redacted] received on 27 April 2020, included the event of contusion that was incorrectly assessed as listed (labelled per the CCDS). Contusion was not listed in the [redacted] CCDS [redacted] dated 23 February 2018 and [redacted] dated 19 October 2020).

Section 43

iii. [redacted] (1): Non-serious spontaneous UK case for [redacted] received on 16 September 2020, included the event sciatica that was incorrectly assessed as unlisted (unlabelled per the CCDS). Sciatica was listed in the [redacted] CCDS [redacted] dated 23 February 2018 and [redacted] dated 19 October 2020).

Listedness assessments were relevant for one of the signal detection processes utilised by Gedeon Richter. 'Index cases' were automatically highlighted as potential signals during the general case processing workflows if they met three criteria: serious, unlisted, and [redacted] causality of 'probable'.

Post-inspection request: As part of the responses to the inspection report, Gedeon Richter should consider the impact of these errors on their signal detection process, and whether any additional pharmacovigilance processes could be impacted by errors in listedness assessments.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

Finding MA.4 e)
One case concerning a prospective report of pregnancy was identified that had not been appropriately followed-up to obtain information relevant for the scientific evaluation of the case. Case [redacted] was a spontaneous German case reporting maternal exposure during pregnancy with [redacted] The latest information for the case was received on 14 May 2020. The MAH stated to inspectors that no follow-up request had been sent as "*latest menstrual period date or expected delivery date unknown*". No request for follow-up information had been sent to obtain the last menstrual period or the expected date of delivery and it was stated by the MAH that the follow-up would be requested "*9 months following the last received date*". Although [redacted] of UK procedure, [redacted] 'Pharmacovigilance System in the United Kingdom and Ireland' [redacted] 12 November 2018) stated "*Follow-up requests should be sent out within 3 working days from LSO's receipt date for non-valid cases and pregnancy cases*", a deviation raised on 28 September 2020 during an internal review conducted shortly prior to the inspection identified that there was no global guidance regarding the timeframes to send requests for follow-up for cases. [redacted] was opened by the MAH to address this deviation, with a corrective action to implement detailed guidance by 07 December 2020.

Section 43

This is a minor finding but has been grouped with the major findings regarding management of adverse events and adverse drug reactions.
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 Documentation of CAPA

Section 43

Finding MI.1 a)
A deviation regarding the training compliance of the case processing vendor, [redacted], had not been recorded formerly in the quality management system. The MAH had identified flaws in the calculation of metrics for training compliance at [redacted] in that training was assigned to all staff irrespective of job function and that metrics calculated may have included staff who were no longer working at the vendor. Although the MAH stated that amendments had been made in August 2020 to allow for more accurate metrics to be compiled, neither the low training compliance figures (which were 55.4% in June 2020 and 50% in August 2020), or the inaccuracy of the metrics calculated, had been raised as a deviation and formally addressed though documented CAPA.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

Section 43

[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Section 43

[redacted]

Finding MI.1 b)
Records maintained by the MAH concerning the resolution of a self-identified non-compliance did not reflect all the actions that had been taken and were inaccurate with regards to the status of implementation. On 03 May 2017, it was identified that information about clinical trials presented by Medical Experts in PSURs did not include all clinical trials for which subject exposure should be provided, according to the requirements of GVP Module VII. This was recorded as non-compliance [redacted] and was documented in PSMF section 14.6 'PSMF Annex G6 - List of in progress critical and major findings and deviations' [redacted], 14 October 2020). On request from inspectors for the current status of actions pertaining to the CAPA plan (inspection request D1), the MAH confirmed that all actions had been completed. However, this was not reflected in the CAPA form provided [redacted] signed 21 March 2018), which showed actions 5 and 6 as uncompleted. To note, action 6 was "*To agree the responsible department for providing requested data about trials during PSUR preparation*". The MAH confirmed that actions 5 and 6 had been completed on 16 May 2018 (over a month after their target date of 03 April 2018). In addition, a new action was included in the response to inspection request D1: "*To start a pilot phase to test the established worksharing*". This action was completed on 31 October 2019 (a year after its anticipated completion date of 31 October 2018), and had not been documented on the non-compliance form. Additionally, the effectiveness check of this CAPA was pending (due on 31 March 2021) and was similarly not reflected on the non-compliance form. As per GVP I.B.11., *"It is recommended that the documentation of the quality system also includes: […] records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventative actions have been taken, that solutions have been applied to deviations and that the effectiveness of the actions taken has been verified".*
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Section 43

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

Finding MI.1 c)
Documentation of CAPA relating to major audit findings in the PSMF lacked the required detail and had not been removed from the PSMF following implementation. PSMF [redacted] 'PSMF Annex G4 – List of Major and Critical Audit Findings' [redacted] 14 October 2020) included a note for the audit of Gedeon Richter Plc. Quality Assurance Department PQC processes (audit ID [redacted] . In the note, the 'deadline for resolution' and 'brief description of CAPA' were stated as 'NA'. The CAPA plans provided on request during the inspection confirmed that all the CAPA had been completed by 30 March 2020, seven months prior to the latest PSMF update. As per GVP II.B.4.7. *"in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). […] The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified".*
Root Cause Analysis
[redacted]

Section 43

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 Collection of adverse events

Finding MI.2 a)
One case reporting adverse events received via a UK patient support programme (PSP) for [redacted] was identified that had incorrectly not been forwarded to Gedeon Richter. The PSP [redacted] was ran by [redacted]. Case [redacted] (2) was a non-serious case, initially received by [redacted] on 16 December 2019 with follow-up information received on 03 January 2020, reporting the adverse events 'Pain', 'Nocturnal awakening' and 'Middle insomnia'. Although this discrepancy was evident from the monthly reconciliation conducted with [redacted] in January 2020, it was only identified during a quality check of documents requested during the inspection.
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MI.2 b)
The January 2020 reconciliation report with [redacted] a business partner responsible for commercialising [redacted] in certain territories including the UK, incorrectly stated that no discrepancies were identified, despite there being numerous discrepancies

between the reconciliation case listings of adverse events and product quality complaints provided by both parties.

Examples of these discrepancies were as follows:

i. [redacted] listing contained 17 case reports, whereas the Gedeon Richter listing contained 16 case reports.
ii. [redacted] listing included case [redacted] and case [redacted] which were not included in the Gedeon Richter listing.
iii. Gedeon Richter listing included cases [redacted] which were not included in the [redacted] listing.

It was confirmed during the inspection that no ICSRs were missed due to the discrepancies, and the identified discrepancies were administrative mistakes made on the reconciliation sheets.

Section 43

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

MI.3 Pharmacovigilance system master file

Finding MI.3 a)
PSMF [redacted] 'PSMF Annex H1 - List of products covered by the global PSMF' (2020 [redacted] 14 October 2020) did not include all territories where [redacted] was authorised. [redacted] was authorised in Singapore on 11 July 2019 to the licensing partner [redacted] As per GVP II.B.4.8, "*An annex to the PSMF shall contain the following documents:* • *A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s), and the Member State(s) in which the authorisation is valid [IR Art 3];*

The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation: […] *- other (non EU) territories where the product is authorised or on the market."*

Section 43

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.4.4 Comments

1. The planned effectiveness check of the CAPA implemented for the self-identified non-compliance [redacted](please refer to [redacted] b), which concerned PSURs missing information for clinical trials, such as subject exposure figures, was to review the number and 'seriousness' of comments from the authorities on the presentation of clinical trials in the assessment report. This is not considered to be an effective measure to verify the completeness of the data, as the PSUR assessor will not have easy access to data to determine whether information on clinical trials and subject exposure is missing. The MAH is therefore advised to reconsider their proposed method for assessing the effectiveness of this CAPA.

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).
- 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 4854/25239-0004	**INSPECTION TEAM**	Beth Webb (lead inspector) Anna Adams
PHARMACOVIGILANCE INSPECTION OF	Gedeon Richter	**DATES**	19 - 22 October 2020

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

- An opening meeting will be held by videoconference on Monday 19 October 2020, which will be led by the lead inspector. The agenda will be as follows:
  - Review of the scope and arrangements for the inspection
  - Gedeon Richter are asked to lead a short company presentation (max. 20 minutes), which aims to provide the inspectors with an overview of the company and pharmacovigilance system. The presentation should focus on the topics listed for inspection and any relevant ongoing remediation work in the pharmacovigilance system.
- The remainder of the inspection will consist of remote document review, written requests and ad hoc video/telephone clarifications with subject matter experts as required. 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.
- A closing meeting will be held via videoconference on Thursday 22 September 2020 (timing to be confirmed) during which feedback on the inspection will be provided to the company. All relevant personnel are welcome to attend the closing meeting.

The inspection will primarily focus on a review of the specific pharmacovigilance activities listed below for [redacted] (cariprazine) and [redacted] (teriparatide)

Topics for review	Personnel (Name & job title)
Topic 1 – ADR management To include, but not limited to: • Case quality in the safety database • Follow-up activities • Quality requirements	GR HQ colleagues (time zone BST + 1 hrs) for the listed subtopics, as follows: **Case quality in the safety database**: [redacted]

Section 40

Section 40

	[redacted]
Topic 2 – Periodic safety update reports To include, but not limited to: • PSUR authoring • Quality control	[redacted]
Topic 3 – Signal management To include, but not limited to: • Signal detection and evaluation activities • Quality requirements	[redacted]

Section 40

Topic 4 – Sources of safety data To include, but not limited to: • Medical information • Product quality complaints • PSPs	[redacted]

Section 40

[redacted]

Gedeon Richter should complete the below with the names and job titles of the designated contact point and those staff who will be joining the opening meeting.

Designated contact point during the inspection: [redacted]

[redacted]

[redacted]