Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: BioMarin Pharmaceutical Inc.

MHRA Inspection Number: Insp GPvP 36300/13675036-0002

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Table of Contents

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
EMA	European Medicines Agency
eRMR	Electronic Reaction Monitoring Report
EU	European Union
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QA	Quality Assurance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
RSI	Reference Safety Information
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Section 40 & 43

Inspection type:	Statutory National Inspection
System(s) inspected:	BioMarin Pharmaceutical Inc., [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted] Schipholweg 73-75, 2316 ZL Leiden, The Netherlands Tel: +31 (0) 71 524 4000 Mobile: +358 504411100 [redacted]
Date(s) of inspection:	21 – 24 September 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	09 – 12 July 2012 01 – 04 February 2011 26 – 28 June 2007
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	Product-specific inspection focused solely on the centrally authorised product, [redacted]
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Adverse Event Management System (AEMS). Comprised of three commercially available software components, [redacted]
Key service provider(s):	- ProPharma Group The Netherlands B.V. provided QPPV services. - ICON Clinical Research provided CRO services for the category 1 non-interventional post authorisation safety study [redacted] A Registry Study) - Medical information services provided by ProPharma Group. - All other critical pharmacovigilance activities were performed in-house by the MAH
Inspection finding summary:	2 Major findings 5 Minor findings
Date of first issue of report to MAH:	27 October 2020
Deadline for submission of responses by MAH:	01 December 2020 Clarifications due 08 January 2021 Further clarifications due 22 January 2021
Date(s) of receipt of responses from MAH:	01 December 2020 Updated responses received 08 January 2021 Updated responses received 22 January 2021
Date of final version of report:	22 January 2021

Section 40

Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

BioMarin Pharmaceutical Inc. 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.

BioMarin Pharmaceutical Inc. (hereafter referred to as BioMarin) is a global pharmaceutical company headquartered in San Rafael (California, USA), which is also the site of the main global pharmacovigilance department (BPV). The role of the EU QPPV is outsourced to ProPharma Group The Netherlands B.V. (Leiden, The Netherlands), and this is also the location of the PSMF.

Section 43

BioMarin focuses on the development of innovative products for rare genetic diseases. The product portfolio in the EU comprises five centrally authorised products: [redacted] and [redacted] This inspection focused solely on [redacted] an orphan medicine authorised via the central procedure in the EU on 28 April 2014 to treat mucopolysaccharidosis type [redacted]

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was specific to the product [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). 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 additional risk minimisation activities, and the collection and collation of safety information from spontaneous and solicited sources (excluding PASS), were not reviewed in detail 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 [redacted] 19 February 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 24 September 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

Not applicable as this was the first MHRA pharmacovigilance inspection of the company since 2012.

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 Post-authorisation safety studies

Requirements:

Directive 2001/83/EC, as amended,
Article 107o *"After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform Member States in which the study is conducted"*

GVP Module V – Risk management systems (Rev 2)
V.C.2.1. *"An RMP update is expected to be submitted at any time when there is a change in the list of the safety concerns, or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimisation activities. The significant changes of the existing additional pharmacovigilance and risk minimisation activities may include removing such activities from the RMP. For example, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials would be expected to be reflected in an updated RMP with the procedure triggering those changes."*

GVP Module VIII – Post-authorisations safety studies (Rev 3)
VIII.A.1. *"Substantial amendment to the study protocol: amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, the study population, the sample size, the study design, the data sources, the method of data collection, the definitions of the main exposure, outcome and confounding variables or the statistical analytical plan as described in the study protocol."*

VIII.B.3. *"In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate should be involved in the review and sign-off of study protocols required in the risk management plan agreed in the EU or conducted voluntarily in the EU (see GVP Module I)."*

A post-authorisation safety study (PASS) is defined in Directive 2001/83/EC, as amended, as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Section 43

The [redacted] category 1 non-interventional PASS, [redacted] Registry Study [redacted] was reviewed as part of this inspection. Category 1 studies are imposed as conditions to the marketing authorisation because they are key to the risk-benefit profile of the product. The observational study was established to characterise and describe the [redacted] syndrome population and to track the clinical outcomes of patients treated with [redacted]. Globally, there are 72 centres involved in the study, with an estimated 457 patients enrolled worldwide; in the UK, there are eight sites with 80 patients enrolled. Data collection was initiated on 27 September 2014. Interim progress reports are produced annually and reported to the EMA, with the final Clinical Study Report expected in March 2025.

The following findings were identified in relation to 110-504 MARS:

Section 43

Finding MA.1 a)
An updated protocol for [redacted] was not submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) for approval following a substantial amendment. [redacted] of the [redacted] protocol (11 June 2014) included the addition of two new sub-studies and corresponding objectives: - To monitor pregnancy exposure, including maternal, neonatal, and infant outcomes. These patients will be encouraged to enrol in the Pregnancy Substudy. - To monitor patients who have completed the [redacted] clinical trials. These patients will be encouraged to enrol in the applicable Registry Substudy and will be monitored using the [redacted] assessment schedules respectively. During the inspection, the MAH confirmed that [redacted] of the [redacted] protocol had not been submitted to the EMA/PRAC for approval; the rationale for this was unknown. Subsequent versions of the protocol did not include any substantial amendments [redacted] was current at the time of the inspection).
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

Section 43

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

Finding MA.1 b)

The [redacted] risk management plan (RMP) was not updated following a substantial amendment to the protocol for [redacted], in which two new sub-studies and corresponding objectives were added (refer to finding MA.1a).

The following sections of the current approved [redacted] 12 February 2014) were out of date with respect to the study objectives for [redacted]

- Section III.5.1 'Table of ongoing and planned studies in the post-authorisation pharmacovigilance development plan'
- Section IV.2 'Summary tables of post-authorisation efficacy studies'
- Section IV.3 'Summary of post-authorisation efficacy development plan'
- Section VI.1.2 'Table of ongoing and planned studies in the post-authorisation pharmacovigilance development plan'
- Section VI.1.3 'Summary of post-authorisation efficacy development plan'
- Annex 6 'Protocols for proposed and ongoing studies in Part III'

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]	

Finding MA.1 c)
There was no evidence that the EU QPPV had reviewed and signed-off any of the five versions of the protocol for [redacted] Appendix A ('Documents requiring EU QPPV review') of [redacted] 'Roles and Responsibilities of the EU QPPV' ([redacted] 12 September 2018) required the EU QPPV to review BioMarin sponsored PASS protocols and amendments, however it was not specified that the EU QPPV was a required signatory. It is acknowledged that this SOP was undergoing revision at the time of the inspection. [redacted] of [redacted] (to be made effective on 01 October 2020) included the requirement for the EU QPPV to be involved in the review and sign-off of protocols for PASS conducted in the EU or pursuant to a risk management plan agreed in the EU.
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]	

MA.2 Management and reporting of adverse events

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
[redacted] Adverse reaction, causality

GVP Module VII – Periodic safety update report (Rev 1)
[redacted] PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"

Finding MA.2 a)

Unrelated adverse events from spontaneous reports were incorrectly reported to competent authorities via expedited reporting of ICSRs and via aggregate reporting in PSUR summary tabulations.

Spontaneous ICSRs containing only adverse events explicitly stated to be unrelated by the reporter and company were incorrectly scheduled for expedited reporting to the EMA. Additionally, adverse events originating from these reports were incorrectly included in the PSUR summary tabulation, 'Appendix 2 - Interval and cumulative adverse drug reactions from post-marketing sources.'

Examples of UK spontaneous cases that were incorrectly reported to the EMA were as follows:

- Case [redacted] Serious report of medical device implantation with [redacted] First received on 10 January 2020 and reported to the EMA on 16 January 2020. The case narrative stated, "*the reporter assessed the event of medical device implantation as not related to treatment with* [redacted] *[…] the procedure was likely performed due to the underlying* [redacted]

Section 43

- Case [redacted] Serious report of knee operation with [redacted] The report was received on 19 February 2018 and reported to the EMA on 26 February 2018. The case narrative stated, "*the reporter assessed the event of knee operation as not related to treatment with* [redacted]

This process was applicable to all products within the BioMarin portfolio. The total number of cases for [redacted] hat appeared to have an unrelated causality assessment from the reporter and company (based on the listing provided in inspection document request [redacted] was approximately 200.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

C.4.3 Minor findings

MI.1 Signal management

BioMarin's signal detection methodology primarily focused on a qualitative approach. Procedural documentation defined the types of evidence that may indicate a signal and highlighted that clinical judgement must be applied. However, examples were identified where clearer documentation of the signal management system would help to ensure proper and effective functioning, and clear and standardised roles, responsibilities and tasks.

Minor deficiencies were identified with regards to the quality requirements for signal management and the requirements for signal management of biological medicinal products, outlined in GVP Product- or population-specific considerations II: Biological medicinal products.

Quality requirements for signal management

Section 43

Finding MI.1 a)
The following deficiencies were identified in relation to the procedural documentation governing the signal detection and management activities at BioMarin: i. [redacted] was included in the pilot on signal detection in EudraVigilance. The electronic reaction monitoring reports (eRMRs) specified the criteria required for drug-event-combinations to be reviewed by the safety physician. However, there was no controlled procedural documentation in place describing the methodology for review of the eRMRs, nor the thresholds used to identify potential signals and the supporting rationale, for the purpose of monitoring the data available in the EudraVigilance database. The monitoring of the available data in EudraVigilance is currently in a pilot phase in the EU. However, it remains a legal requirement for 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. ii. The signal detection plan for [redacted] October 2017) did not include the quarterly review of the eRMR in EudraVigilance. iii. BioMarin's signal detection strategy included the qualitative review of ICSRs during case processing and the quarterly qualitative review of aggregate safety data. [redacted] 'Signal Detection for BioMarin Investigational and Marketed Products' [redacted] 15 May 2020) described that potential safety signals from the aggregate data may be identified from changes in frequency, severity, or patient distribution. However, the SOP did not specify any thresholds in relation to frequency, severity or patient distribution that might indicate when a potential signal required further evaluation from the aggregate review.
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment
[redacted]

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

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

Signal management for biological medicines

Finding MI.1 b)
Minor deficiencies were identified with regards to BioMarin's approach to signal detection for biological medicines. BioMarin conducted an Annual Product Review for each of their commercialised products to summarise and evaluate manufacturing, process control, and quality data. The BioMarin pharmacovigilance team contributed to the Annual Product Review of [redacted] in accordance with [redacted] *'Annual Product Review'* ([redacted] 23 March 2020) by reviewing all

adverse events and product technical complaints received in the report interval in the context of associated batch numbers to identify any safety concerns related to product quality.

The following limitations with the approach were identified:

i. There was no evidence that all cases received cumulatively for a specific batch were reviewed, only those within the report interval. Thus, the review did not cover the entire lifecycle of a batch (the unopened product had a shelf life of three years).

ii. Batch-specific exposure data were not included in the review to identify whether there were any changes in the adverse event reporting rate for specific batches. It was explained verbally during the inspection that the overall exposure data presented in the PSUR was considered when reviewing the adverse event data.

Section 43

iii. According to [redacted] "*Pharmacovigilance is responsible for providing the following: […] A summary of all Adverse Event (AE) data potentially related to product quality since the last product review, including the number, type, and follow-up actions if any.*" However, the SOP did not provide further information on the methodology used for reviewing the adverse event data and associated batch numbers.

BioMarin are reminded of the guidance outlined in section B.4. 'Signal management' of GVP Product- or Population-Specific Considerations II: Biological medicinal products, which states:

"*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 […]*

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)."

Root Cause Analysis

[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.1 c)

[redacted] *Signal Detection for BioMarin Investigational and Marketed Products'* [redacted] 15 May 2020) did not include the requirement that signals identified for biological medicinal products should be evaluated in the context of batch-specific exposure data.

As outlined in [redacted] "*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.*"

To note, at the time of the inspection, no signals requiring evaluation had been identified for [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

Section 43

[redacted]

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

MI.2 Pharmacovigilance system master file

Finding MI.2 a)

The version of the PSMF and annexes provided for review during the inspection did not include up to date information on the current pharmacovigilance system.

[redacted] of [redacted] 06 June 2019) stated that if the PSMF was requested by Health Authorities or regulatory inspectors (within seven days), BioMarin Pharmacovigilance (BPV) will process minor changes (e.g. updates to the annexes) and a new version of the PSMF will be provided. However, on request of an up to date PSMF prior to the inspection (04 September 2020), it was confirmed that [redacted] of the PSMF and annexes (dated 19 February 2020) was the current version.

Although the MAH confirmed that there had not been any significant updates to the PSMF since this date, information held within the annexes was out of date. For example, 'Annex F – Pharmacovigilance System Performance' only included metrics data up to December 2019.

The MAH is reminded of the legal requirement outlined in Article 104(3)(b) of Directive 2001/83/EC, as amended, to maintain and make available on request a pharmacovigilance system master file, and the requirement in Article 1(1) of Commission Implementing Regulation (EU) No 520/2012 that information in the pharmacovigilance system master file shall be accurate and reflect the pharmacovigilance system in place.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

Section 43

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

Preventative Action(s)

[redacted]

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

Finding MI.2 b)

Information in the current PSMF [redacted] 19 February 2020), [redacted] 'Significant open PV external audit findings', did not accurately reflect the actual status of major audit findings, despite the status being updated prior to the most recent PSMF update.

An audit of [redacted] a CRO involved in the management of three BioMarin sponsored studies, was conducted on 09 - 10 May 2019. Four major findings were identified, two of which concerned the conduct of [redacted] (findings [redacted] and [redacted] For both findings, [redacted] of the PSMF stated that the "*Corrective and Preventative Action plan(s) are to be agreed*". However, the CAPA plans for these audit findings were finalised on 26 December 2019, and closed on 13 and 14 February 2020, respectively.

Root Cause Analysis

[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 c)

Completed audits of entities providing pharmacovigilance-relevant services associated with the category 1 non-interventional PASS [redacted] had not been included in the BioMarin PSMF Annex G – 'Quality System', [redacted] '2016 to 2020 GVP Compliance Audit Schedule' [redacted] 19 February 2020). Examples included:

- Two audits of [redacted] (CRO), conducted 30 – 31 March 2017 and 9 – 10 May 2019
- Site audits of [redacted] (conducted 15 – 17 May 2019), [redacted] (conducted 05 - 06 June 2019) and [redacted] conducted 18 - 20 June 2019)

It was confirmed that these audits formed part of the GCP compliance audit schedule, and hence had not been considered for inclusion in the PSMF. The MAH is reminded that all

Section 43

scheduled and completed audits relevant to the pharmacovigilance system should be documented in an Annex to the PSMF in line with Article 3(5) of Commission Implementing Regulation (EU) No 520/2012. To note, the major findings identified during these audits were documented in PSMF [redacted] 'Significant open PV external audit findings'.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MI.2 d)
A list of tasks that had been delegated by the EU QPPV was not included in the BioMarin

Section 43

PSMF Annex A – 'The Qualified Person responsible for Pharmacovigilance' [redacted] 19 February 2020).

As an example, senior management of the BPV team participated in the Annual Product Review data meeting, following which any product quality issues would be fed back during regular meetings with the QPPV; however, this was not documented in Annex A of the PSMF.

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.3 Data management

Finding MI.3 a)

Summary tabulations of adverse events presented in the interim progress report for study [redacted] Annual Report 2020' (covering the period 14 February 2019 – 13 February 2020) referred to three 'unmapped' events. The report, which was submitted to the EMA, did not include any description or explanation of these events.

The following tables were affected:

- Table 6-13 'Incidence of adverse events by System Organ Class'
- Table 6-14 'Adverse events by preferred term and severity'
- Table 6-15 'Incidence of treatment-emergent serious adverse events by preferred term'

It was confirmed during the inspection that the three unmapped terms related to adverse events that had been received or updated prior to creation of the database output, but that had not yet been coded. The unmapped terms referred to the below events:

- [redacted] – Suspected device infection
- [redacted] – Hospitalisation for wisdom tooth extraction
- [redacted] – Worsening of bilateral genu valgum

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]	

Section 43

MI.4 CAPA management

Finding MI.4 a)
There was a significant delay in raising a CAPA record in the QA system to document late ICSR submissions. In 2018, during close-out activities with [redacted] a patient support programme vendor in [redacted] it was identified that 59 adverse events dating from circa 2017 had not been reported to BPV. Following a thorough review, it was determined that the vendor had used an incorrect email address to notify BPV. As a result, there were three late competent authority submissions. Although a Department Note to File was created and archived to document this incident and corrective action had been carried out and completed as of 2018, a CAPA record was not opened until 03 September 2020 (record ID, [redacted], after announcement of the MHRA inspection. [redacted] of [redacted] 'Process for the management of late case CAPA' (first effective 24 August 2012) required a CAPA record to be created within five days of awareness that a late submission had occurred.
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.5 Procedural documentation

Finding MI.5 a)
There was no documented procedural timeline between the approval of reference safety

information (RSI) and the subsequent distribution to relevant personnel.

RSI distribution was owned by regulatory affairs, who used a link to distribute current RSI around the company. This process was described in the regulatory affairs Labelling Implementation SOP; however, the procedure did not stipulate the maximum amount of time that could elapse between approval of RSI and association of the RSI with the link. No evidence of a significant delay between approval of RSI and distribution was observed during the inspection.

Section 43

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

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

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

The 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".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 36300/13675036-0002	**INSPECTION TEAM**	Beth Webb (lead inspector) Sophie Radicke Dominic Nguyen-Van-Tam
PHARMACOVIGILANCE INSPECTION OF	BioMarin	**DATES**	21 - 24 September 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 Friday 18 September 2020 at 3.30pm BST (to accommodate the distribution of personnel across different time zones), which will be led by the lead inspector. The agenda will be as follows:
  - Review of the scope and arrangements for the inspection
  - BioMarin 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 24 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 be focused on a review of the specific pharmacovigilance activities listed below for Vimizim (elosulfase alfa)

Topics for review	Personnel (Name & job title)
Topic 1 – ADR management To include, but not limited to: • ICSR management and submission to EudraVigilance • Case quality in the safety database • Follow-up activities	**BioMarin PV (BPV), PST time zone:** [redacted]

Section 40

Section 40

Topic 2 – Periodic safety update reports To include, but not limited to: • PSUR authoring • Quality control	**BPV, PST time zone:** [redacted]
Topic 3 – Signal management To include, but not limited to: • Signal detection and evaluation activities • Quality requirements	**BPV, PST time zone:** [redacted]
Topic 4 – Post-authorisation safety studies To include, but not limited to: • Collection and management of safety data • Generation of interim study reports • Quality assurance and vendor oversight	**BPV, PST time zone:** [redacted]

BioMarin 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]

Opening meeting attendees:

GxP Compliance (PST time zone):

Section 40

[redacted]