Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Bausch Health Group

MHRA Inspection Number: Insp GPvP 3468/14918-0008

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Table of Contents

ABBREVIATIONS

ADR	Adverse Drug Reaction
aRMM	Additional Risk Minimisation Measures
CAPA	Corrective and Preventative Action
DLP	Data Lock Point
DMRC	Defective Medicines Reporting Centre
EMA	European Medicines Agency
EOE	Evaluation of Effectiveness
EU	European Union
GPRM	Global Pharmacovigilance and Risk Management
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
PSC	Product Specific Convention
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SDR	Signal of Disproportionate Reporting
SOC	System Organ Class
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Section 40 & 43

Inspection type:	Statutory National Inspection
System(s) inspected:	Bausch Health Group, MFL 5096
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	Remote inspection: 22 April 2020 – 30 June 2020 (total: 5 inspection days)
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	n/a
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 adrenalin auto-injector, [redacted]
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	LifeSphere Safety MultiVigilance (LSSMV) (ARISg)
Key service provider(s):	Pharmacovigilance services provided by Bioclinica, including evaluation and processing of safety data, aggregate reports, risk management plans, literature searching and audit services. Medical information services provided by [redacted] (contract terminated June 2019).
Inspection finding summary:	1 Critical finding 1 Major finding 1 Minor finding
Date of first issue of report to MAH:	21 July 2020
Deadline for submission of responses by MAH:	25 August 2020 Clarifications due 21 September 2020
Date(s) of receipt of responses from MAH:	25 August 2020 Updated responses received 18 September 2020
Date of final version of report:	02 October 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Bausch Health Group 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.

Bausch Health Group is a multinational company headquartered in Quebec, Canada that develops, manufactures and markets a broad range of branded and generic pharmaceuticals. Pharmacovigilance is organised globally with sites in several regions and countries. Bausch & Lomb UK Limited is a UK affiliate of the Bausch Health Group. The EU QPPV is based in Berlin, Germany, which is where the PSMF is located.

Many pharmacovigilance activities are performed in-house; however, outsourced activities to the main service provider, Bioclinica, include the evaluation and processing of safety data, literature search activities, audit support, and the composition of aggregate reports.

The company holds licenses for 58 products in the UK, of which 12 are authorised via a centralised procedure and the remaining are authorised nationally, via a mutual recognition (MRP) or a decentralised procedure. Globally, the product portfolio is focused on dermatology, eye health, gastrointestinal disorders and neurology, while the focus in the UK is primarily vision care.

Section 43

[redacted] adrenalin auto-injectors are licensed in the UK via an MRP (first authorised, 03 January 2013) and marketed by [redacted] an affiliate within the Bausch Health Group. In September 2019, Direct Healthcare Professional Communications were issued, followed by multiple product recalls between November 2019 and May 2020, in the UK. These safety measures were implemented as a result of the risk of [redacted] pens failing to activate. Further details regarding the investigation are provided in section C.4.1.

B.2 Scope of the inspection

The inspection was product-specific and focused solely on pharmacovigilance activities relating to [redacted] adrenalin auto-injectors. Particular focus was paid to pharmacovigilance aspects of the handling of reports of auto-injector activation issues and the product recalls, as well as the implementation of agreed additional risk minimisation measures (aRMMs).

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).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version 18.0, 31 January 2020) to assist with inspection planning and preparation. 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 30 June 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.

C.2 Definitions of inspection finding gradings

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

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

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

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

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

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

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

CR.1 Ongoing safety evaluation

Section 43

On 21 August 2019, an investigation into [redacted] pens failing to activate was initiated by the MAH. A cross functional team was put in place to lead and support the investigation, and root cause investigations were conducted in collaboration with the auto-injector manufacturer ([redacted] the [redacted] finished product manufacturer [redacted] and [redacted] (experts in auto-injector technology).

As a result of the risk to patients from the pens failing to activate, a Class 2 Medicines recall of all [redacted] products was issued by the MHRA on 28 November 2019 in the UK, and further Class 2 Medicines recalls at a patient-level for each strength of [redacted] pen [redacted] were issued by the MHRA on 04 March, 07 April and 18 May 2020 in the UK.

There were fundamental weaknesses in the MAH's pharmacovigilance processes that contributed to a delay in identifying and rectifying this safety issue, and accordingly represent a breach of the MAH's legal obligation to *"evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary"*, in accordance with Article 104(2) of Directive 2001/83/EC, as amended. This significant breach of legislation, and the potential impact on public health and patient safety posed through a failure to take timely action, has resulted in the issuing of a critical finding in the area of ongoing safety evaluation.

Multiple elements contributed to the critical finding, with deficiencies identified in the following areas:

- Signal detection and considering options for risk minimisation
- Management of product quality issues
- Written procedures

The investigation into [redacted] pens failing to activate remains ongoing. Proposed corrective actions by the MAH include a planned re-introduction of the product to the market following alterations to the auto-injector components. In light of the ongoing quality defect investigation, details of the complaint reports obtained during the inspection have been shared with colleagues in the Licensing Division at the MHRA.

Requirements:

Directive 2001/83/EC as amended,
Article 104 (1) *"The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under Article 101(1)."*

Article 104 (2) *"The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary."*

Article 107 (1) *"Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.*

Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union."

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."*

GVP Module IX – Signal management (Rev 1)
IX.B.1. "*Signals can arise from a wide variety of data sources. This potentially includes all scientific information concerning the use of medicinal products and the outcome of the use, i.e. quality, non-clinical and clinical data (including pharmacovigilance and pharmacoepidemiological data)."*

IX.B.2. *"Signal detection should follow a methodology which takes into account the nature of data and the characteristics (e.g. time on market, patient exposure, target population) as well as the type of medicinal product concerned (e.g. vaccines and biological medicinal products may for example require specific methodological strategies (see GVP P.I. and GVP P.II.)). Data from all appropriate sources should be considered (see IX.B.1.)."*

IX.B.3. *"The following elements should be considered when performing signal validation based on the review of ICSR data […]*
Strength of the evidence, taking into account, e.g.:
- the total number of cases (after exclusion of duplicates), and amongst those, the number of supportive cases, e.g. cases showing a compatible temporal association, positive de- or rechallenge, lack of potential alternative causes, assessed as possibly related by the reporting healthcare professional, with supportive results of relevant investigations;
- number of cases in the context of patient exposure"

IX.B.5. Quality requirements "*Signal management is considered a critical process (see GVP Module I). 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 […] Through a tracking system, all organisations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale."*

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.6.4. "*In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame (see VI.C.6.2.3.4. for EU guidance on the management of these ICSRs). Medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases. This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicinal product."*

Section 43

Prior to 21 August 2019, when Bausch first initiated the investigation into [redacted] pens failing to activate, the company had received 28 product quality complaints (earliest report, 05 January 2016) that described [redacted] pens failing to activate or other synonymous terms. These had all been classified as 'unconfirmed' by the MAH and the finished product manufacturer ([redacted] as the manufacturer was unable to physically verify the reports of the pens failing to activate. The complaints included two reports of fatal

outcomes. 'Unconfirmed' complaints included those where the sample was unavailable for testing, those where the complaint sample pen had been received already activated and cases where the manufacturer was able to activate the pen during testing.

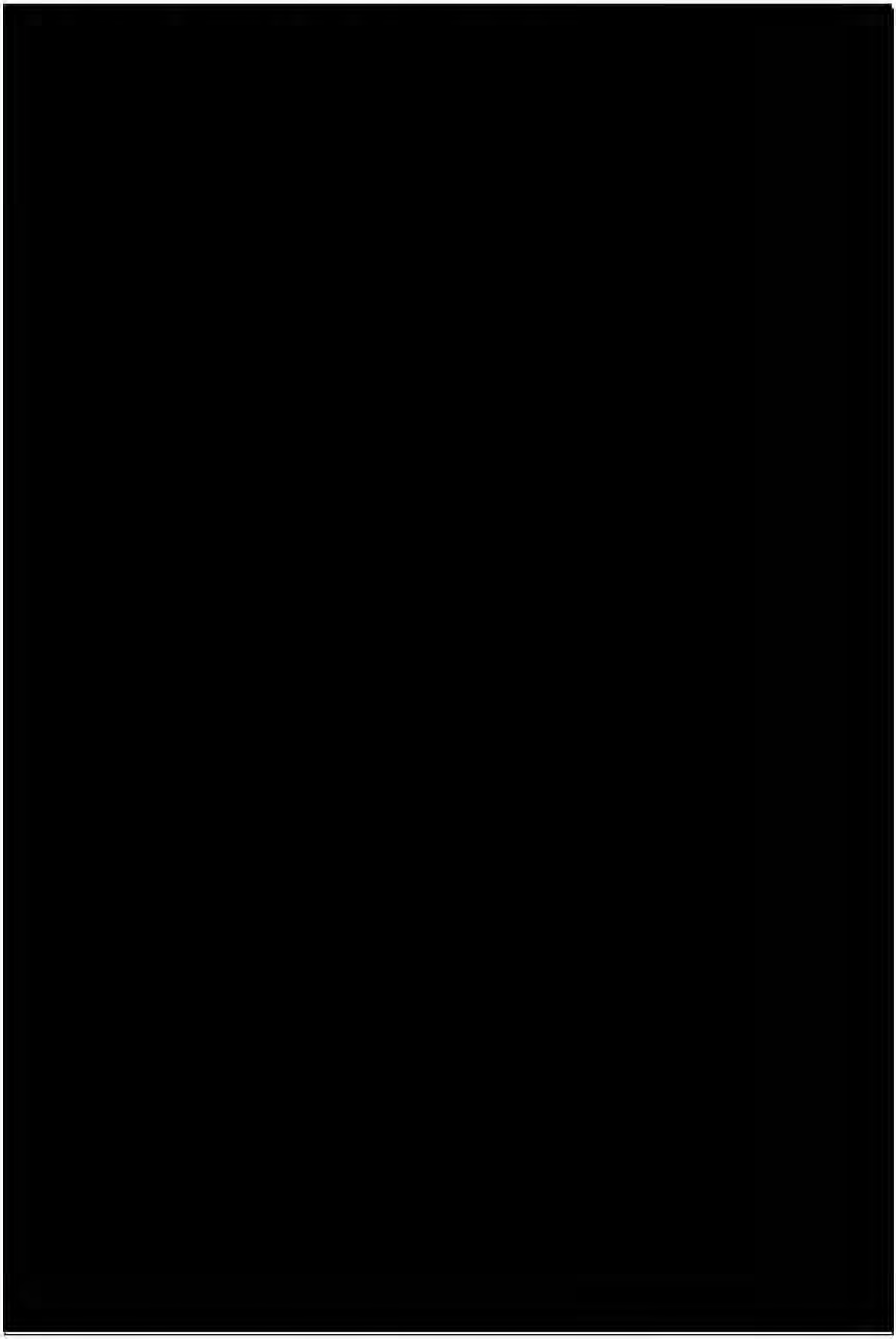
Only upon receipt of a complaint sample (in August 2019) that did not trigger as expected on the first test fire by the manufacturer, was the complaint classified as 'confirmed' and an investigation was initiated. This was seven days after the MAH had been contacted by the Defective Medicines Report Centre (DMRC) within the MHRA on 14 August 2019 raising concern of three similar reports received via the Yellow Card Scheme. It should be noted that the pen in the index 'confirmed' case was successfully activated on the second attempt by the manufacturer.

Section 43

Many of the previous complaints had been attributed by the MAH to incorrect patient handling and usage of the [redacted] pens. Additional risk minimisation materials (aRMMs) for [redacted] were required as per the risk management plan (RMP) to inform healthcare professionals, patients and caregivers of the risk of drug administration error, including accidental injection, lack of drug effect and auto-injector not working in a critical situation.

Finding CR.1 a)
Despite the receipt of numerous complaints reporting the failure of [redacted] auto-injectors to activate, of which many had been attributed by the MAH to incorrect patient handling and usage, the company neither raised a signal of a potential product quality issue nor considered whether there was a need to take further measures based on the effectiveness of their aRMMs. GVP Module IX requires that the signal detection methodology takes into account the nature of data and the characteristics (including patient exposure) as well as the type of medicinal product concerned. As [redacted] pens are indicated for the emergency treatment of severe allergic reactions (anaphylaxis), only a small percentage of [redacted] pens are ever actually used by patients, and therefore the threshold at which action is taken by the MAH should be low, particularly in light of the severity of the risk of auto-injectors failing to activate. The effectiveness of [redacted] aRMMs was reviewed by the MAH in April 2019 through an Evaluation of Effectiveness (EOE) report (DLP, 31 October 2018), in which adverse event reports concerning the risk of drug administration errors were reviewed. In total, 28 relevant reports were identified (eight reports did not specify brand), of which eight reports were from the UK. The EOE report was contradictory in stating "*some* [issues] *can be related to patient education and their understanding regarding administration and usage of this medicine*", yet concluded by stating "*there is no reason to consider that any of the additional risk minimisation measures are ineffective in reaching their objective*". No further consideration of aRMM effectiveness was undertaken by the MAH, despite an increase in the number of complaints received after production of the EOE report. To note, the next planned EOE report was postponed due to the product recalls. As per Directive 2001/83/EC as amended, Article 104(2), MAHs are required to evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.
Root Cause Analysis
[redacted]

Section 43



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 CR.1 b)
Complaint trend analysis was not being conducted as required by SOP [redacted] 'EMQA Complaints Management' (12 April 2019). Version 04 of SOP [redacted] included the addition of the following requirement: *"an investigation report must include as a minimum [...] complaint trend analysis (summary of other complaints already received on same batch, same product, and/or same reason)".* Prior to April 2019, complaint trend analysis was not routinely conducted as part of product quality complaint investigations, and evidence of this activity conducted after April 2019 was inconsistent. For example, trend analysis for complaint [redacted] (received 24 May 2019), which reported an [redacted] pen failing to activate, was not conducted during the complaint investigation (dated 30 August 2019 by [redacted] It is acknowledged that the complaint was included in the trend analysis summary reports as part of the wider [redacted] failure to activate investigation, which were produced in September 2019, October 2019 and February 2020. Section 8.19 of Eudralex, Volume 4, Part I, Chapter 8 (The Rules Governing Medicinal Products in the European Union, August 2014) states "*Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.*"

Section 43

Although the requirement to conduct trend analyses of quality defect records falls on the manufacturer, the MAH is encouraged to review their current procedures and practices regarding complaint trend analysis with the relevant manufacturer(s) in order to ensure that robust analyses are being conducted with the ability to identify potential emerging safety issues should they arise.
Root Cause Analysis
[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 CR.1 c)
The MAH had introduced product specific conventions for [redacted] reports on 22 June 2018

that stated "*All lack of effect or device use issue/malfunction where the patient could not be administered the product must be made as life threatening events and subject to reporting because this product is typically given for emergency anaphylactic reaction treatment.*" However, it was not until January 2019 when the MAH decided to enter all product technical complaints concerning patients who were unable to use the product due to a technical issue into the global safety database. No retrospective review of relevant reports was conducted.

Section 43

During the inspection it was identified that five reports where the patient was unable to use an [redacted] pen due to a technical issue had not been recorded as pharmacovigilance-relevant reports within the global safety database, and subsequently were not included in routine signal detection nor considered for submission to EudraVigilance:

- [redacted]

As [redacted] is indicated for the treatment of anaphylaxis, a critical life-threatening condition, reports where patients are unable to use the medication due to a technical issue should be handled in line with GVP VI.B.6.4., as serious ICSRs and submitted to EudraVigilance within 15 working days.

Of the five examples identified, one complaint was received after implementation of both conventions.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Section 43

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

Section 43

Finding CR.1 d)
Three reports were identified that had been incorrectly excluded from the root-cause investigation into [redacted] pens failing to activate that was initiated in August 2019. To identify relevant reports for inclusion in the investigation, complaints were selected manually from a listing of all [redacted] product technical complaints based on the complaint description. The following complaints were not selected for inclusion, despite there being a suspicion that the pens failed to activate: • Case [redacted] (version 1): Serious, spontaneous report from France, initially received as a product technical complaint [redacted] on 27 June 2018. Case narrative stated, *"The patient used the first pen of [redacted] normally in response to the symptoms and without any problem. After that, as there was no improvement on her symptoms, the patient tried to use the second pen of [redacted] …] but the pen's mechanism was not triggered (device failure)."* • Case [redacted] (version 3): Serious, spontaneous report from Germany (fatal outcome), initially received via the German Health Authority on 28 September 2018. Source documentation (received via a phone call) stated, *"it is suspected that the [redacted] pen did not trigger".* It is acknowledged that during the quality investigation, which was conducted in the presence of the German Health Authority, the [redacted] auto-injector was successfully activated; however, this this was not considered a sufficient reason to exclude the report from the investigation. Other complaint samples that were successfully activated by the manufacturer during complaint investigation have been included in the failure to activate root-cause investigation. • Case [redacted] (version 1): Serious, spontaneous report from Germany, initially received 06 August 2019. Source documentation stated, *"customer complains that this did not trigger despite correct application, and the solution escaped from the side of the injector pen"*. The justification for exclusion of this report provided by the company was based on the description of the solution escaping from the side of the injector pen. This was not considered sufficient to exclude this report from the root-cause investigation.
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)
[redacted]

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

Section 43

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

Finding CR.1 e)
Inaccuracies in the data available in the agBalance signal detection software resulted in outputs that did not contain all relevant and up to date information to support the signal detection process. In October 2019, an internal review of event coding in [redacted] reports was conducted following initiation of the activation failure investigation. In order to standardise how reports of failure to activate were captured in, and therefore retrievable from, the global safety database, any reports indicating that the pen did not trigger properly, failed to activate, was faulty or locked, were re-coded to the [redacted] 'Device malfunction'. However, the re-coded reports were not resubmitted to agBalance signal detection software. As such, the monthly signal detection outputs for epinephrine [redacted] were inaccurate with regards to the true number of cumulative cases and the subsequent disproportionality calculations. For example, the epinephrine signal detection output for April 2020 listed the cumulative number of reports with the PT 'Device malfunction' as 43, however, the total number of device malfunction reports associated with [redacted] in the global safety database, based on an output from 31 March 2020, was 67. A major and minor finding have been reported regarding the conduct of the re-coding project (please refer to MA.1 and MI.1).
Root Cause Analysis
[redacted]

Section 43

[redacted]

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

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

Finding CR.1 f)
Written procedures on signal detection lacked detail and hence there was no standardised process to document the review, analyses and decisions made relating to signals of

Section 43

disproportionate reporting (SDRs).

A signal detection tool query within agBalance software generated listings of SDRs that met the threshold defined in [redacted] Reference Document (revision 2, 17 August 2018). [redacted] Signal Management Procedure (revision 8, 06 March 2020) stated that the GPRM Risk Management Team were responsible for conducting review of the SDRs in the signal detection tool, however there was no further instruction detailing which SDRs required review or how this review should be performed and documented.

The review of a small number of SDRs had been documented using annotations within [redacted] which provided the status of the SDR (i.e. close monitoring, confirmed signal etc.). [redacted] Reference Document included instructions on how to add an annotation to SDRs on agBalance; however, there was no guidance as to which SDRs required annotation. Of the 53 SDRs in the April 2020 epinephrine output, only three had been annotated.

During the inspection, it was confirmed verbally that:

- SDRs with no new reports for that interval did not require review.

- New SDRs that had not been flagged in previous intervals would be reviewed in-depth:
  - This was evidenced for the SDR of 'Kounis syndrome' in the April 2020 epinephrine [redacted] signal detection output, where evidence of in-depth review was documented on the activity log in [redacted] However, in-depth review was not evidenced for other new SDRs in epinephrine signal detection outputs (i.e. 'Needle issue' and 'Product prescribing error' in March 2019; 'Feeling hot' and 'Septic shock' in March 2020).

- New reports for SDRs that had been flagged in previous intervals would be reviewed:
  - For the requested epinephrine signal detection outputs (March 2019 and March 2020), an informal Excel document had been used to record comments for the SDRs. These documents could be uploaded to [redacted] however there was no guidance on when upload was necessary or what level of detail was required within the review.

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]	

C.4.2 Major findings

MA.1 Adverse Drug Reaction (ADR) management and reporting

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)
VI.C.6.2.2.8. Amendment of cases "*Serious and non-serious cases which have already been submitted to EudraVigilance may need to be amended when, after an internal review or according to an expert opinion some items have been corrected, without receipt of new information that would warrant for the submission of a follow-up report.*
Where the amendment significantly impacts on the medical evaluation of the case, an ICSR should be resubmitted and information on the amendment should be explained in the case narrative. For example, an amendment of the MedDRA coding due to a change in the interpretation of a previously submitted ICSR may constitute a significant change and therefore should be resubmitted as amendment report"

Finding MA.1 a)

Section 43

There was a failure to resubmit ICSRs to EudraVigilance following case amendments that impacted the way events were presented in the case.

As a result of the internal review of event coding in [redacted] reports conducted in October 2019 (refer to CR.1 e), events in 31 reports were re-coded for consistency to the MedDRA PT 'Device malfunction' on the global safety database. However, the MAH incorrectly considered these changes to be medically insignificant, and as such these reports were not resubmitted to EudraVigilance as case amendments.

In some examples, coding amendments of the [redacted] PTs resulted in a change to the [redacted] SOC mapping, which would affect the presentation and assessment of data in PSURs, as well as the retrieval of cases in relevant searches conducted by authorities in EudraVigilance. Examples included:

- [redacted] (version 1): Serious spontaneous report from Germany, initially received 19 July 2019 and submitted to EudraVigilance on 30 July 2019. It was reported in the case narrative that "*assistant physician applied the* [redacted] *with no therapeutic effect (lack of drug effect) the needle came out, but the patient did not feel the injection of the solution (the needle hit into the flesh but the injection solution didn't came out), furthermore, the needle was completely dry […]* [redacted] *pen was used correctly and the needle was also extended, but the Emerade medication remained inside the* [redacted] *pen and was not injected into the patient*". The submitted case contained two events coded as 'Drug use issue', an LLT that falls under the Injury, poisoning and procedural complications SOC, and 'Lack of efficacy', an LLT that maps to the PT 'Drug ineffective'. The PTs in the case in the global safety database were 'Device malfunction', which falls under the Product issues SOC and 'Drug ineffective'.

- [redacted] (version 0): Serious spontaneous report from Austria, initially received 04 July 2018 and submitted to EudraVigilance on 16 July 2018. It was reported in the case narrative that "*the patient was not able to release the* [redacted] *[…] several attempts were necessary to use the* [redacted] The submitted case contained one event coded as 'Device use issue', an LLT that falls under the Injury,

poisoning and procedural complications SOC. The PT in the case in the global safety database was 'Device malfunction', which falls under the Product issues SOC.

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)**

Section 43

[redacted]

Finding MA.1 b)

Two reports were not re-coded to include the [redacted] 'Device malfunction', as a result of the internal review of event coding in [redacted] reports (refer to CR.1 e and MA.1 a), despite describing a failure of [redacted] pens to activate:

- Case [redacted] (version 0): Serious spontaneous report from the UK, initially received 25 July 2019 and submitted to EudraVigilance on 02 August 2019. Source documentation included the following statement, "*The first pen […] failed to deliver a dose as there was no "clicking" sound and great force had to be used and nothing happened*". Three PTs were coded in the case as 'Device occlusion', 'Device defective' and 'Expired product administered'.

- Case [redacted] (version 3): Non-serious spontaneous report from Germany, initially received 21 January 2019, but not submitted to EudraVigilance as adverse event occurrence was associated with training pen usage. Source documentation included the following statement, *"I've mentioned several times that this is regarding a broken pen […] otherwise I would not have noticed that it did not trigger"*. One PT was coded in the case as 'Device occlusion'.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

C.4.3 Minor findings

MI.1 Procedural documentation

Section 43

Finding MI.1 a)
There was a delay of five months between implementing [redacted] specific coding conventions and updating the Product Specific Convention (PSC) Document. Following the internal review of event coding in [redacted] reports (refer to CR.1 e and MA.1), an email was sent to relevant associates on 08 October 2019 with new coding guidance that stated, *"Going forward, any reports of the pen not triggering properly/failed to activate/pen faulty/pen locked (or similar events) should be coded to 'device malfunction'"*. However, the PSC Document was not updated until five months later on 06 March 2020. The PSC Document was uploaded on the MAH's Learning Management System (ComplianceWire) for the training of each relevant associate after each update.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
[redacted]
Preventative Action(s)
[redacted]

Section 43

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.

Section 43

In light of the ongoing quality defect investigations into activation failure of [redacted] details of the complaint reports obtained during the inspection were shared with colleagues in the Licensing Division at the MHRA. Additionally, this inspection has been referred to the Inspection Action Group for GCP and Pharmacovigilance (IAG) at the MHRA, agreed outcomes of which are detailed below.

D.2 Recommendations

Given the seriousness of the inspection findings, the Inspection Action Group for GCP and Pharmacovigilance (IAG) has recommended that the next MHRA pharmacovigilance inspection is performed prior to the relaunch of [redacted] on the UK market, to review the impact of the actions taken in response to the inspection findings. Please note that this inspection may be conducted unannounced or at short notice.

In addition, the MAH is requested to provide monthly updates to the lead inspector on the status of deliverables related to the corrective and preventative actions agreed in the responses to the critical and major finding in the inspection report, and the status of [redacted] relaunch activities for the UK market. Updates should be provided to the lead inspector by email on the first day of each month (commencing 01 November 2020).

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).
- 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.
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- Eudralex Volume 4, Part I, Chapter 8: The Rules Governing Medicinal Products in the European Union – EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use, August 2014

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Bausch & Lomb	**DATES**	w/c 20 April - June 2020
Inspection plan			

Section 43

This inspection will be product-specific and will focus solely on [redacted] adrenalin auto injector.

As a remote inspection, an opening meeting will be held via teleconference. This will be followed by a period of inspector document request and review; deadlines for providing document requests to the inspectors will be specified by the lead inspector but will be no less than 7 days. The lead inspector will provide notification of when the remote inspection is complete and will organise a closing meeting teleconference to provide feedback on any non-compliance identified.

Interview sessions with company personnel are not envisioned. However, we request that you provide a designated contact point who can assist with any ad hoc questions from inspectors or arrange calls between inspectors and SMEs as required.

Bausch & Lomb should complete the below with the names and job titles of those staff who will be dialling in to the opening meeting and the designated contact point.

Bausch & Lomb designated contact point: [redacted]
Local Responsible Person for Pharmacovigilance (LPPV);
Pharmacovigilance and Medical Information Officer
[redacted]

Section 40 & 43

Opening meeting: w/c 20 April 2020

There will be an opening meeting to review the scope of the inspection. Bausch & Lomb are asked to lead a company presentation which aims to orientate the inspectors around the company, the pharmacovigilance system and the quality system. This presentation should last no longer than 20 minutes.

The company are requested to provide an overview of the ongoing and completed investigations and actions relating to [redacted] pens and the failure to activate, which has resulted in two UK recalls. This can be included as part of the company presentation during the opening meeting, or a stand-a-lone presentation can be organised if required.

Bausch & Lomb Opening meeting contact list

[redacted]

Topics

- Pharmacovigilance oversight of the investigations relating to the [redacted] recalls
- Management of [redacted] reports, product quality complaints and medical information enquiries
- [redacted] additional risk minimisation measures
    - Procedural documentation, tracking mechanisms and dissemination records

Closing meeting: date tbc

A closing meeting will be held via teleconference. The date and timing of this meeting will be communicated in due course by the lead inspector.