Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Alexion Pharma UK

MHRA Inspection Number: Insp GPvP 31187/19028368-0001

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ABBREVIATIONS

ADR	Adverse Drug Reaction
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CoV	Certificate of Vaccination
CSR	Clinical Study Report
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
eCRF	Electronic case report form
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PIL	Patient Information Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QPPV	Qualified Person responsible for Pharmacovigilance
REC	Research Ethics Committee
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreement

SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
UK	United Kingdom
US	United States

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Alexion Pharma UK, [redacted]
Site(s) of inspection:	Alexion Pharma UK 3 Furzeground Way, Stockley Park, Uxbridge, Middlesex UB11 1EZ
Main site contact:	[redacted] Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard 5th Floor Boston MA 02210 USA [redacted]
Date(s) of inspection:	16 – 19 September 2019. Office-based document review continued after the site visit and was concluded on 02 October 2019.
Lead Inspector: **Accompanying Inspector(s):**	[redacted]
Previous inspection date(s):	12 – 13 May 2015
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the general systems review, specific ADR reports and PSURs were examined for [redacted] [redacted] and Kanuma (all CAPs).
Name and location of EU QPPV:	[redacted] Alexion Europe SAS 103-105 rue Anatole France 92300 Levallois-Perret France [redacted]
Global PV database (in use at the time of the inspection):	Name of system: Argus version 7.0.3.1 (commercially available)
Key service provider(s):	ICSR management and aggregate reporting writing services provided by PPD. Medical information services provided by ProPharma Group.
Inspection finding summary:	0 Critical findings 4 Major findings 3 Minor findings
Date of first issue of report to MAH:	12 December 2019
Deadline for submission of responses by MAH:	24 January 2020, extension agreed until 07 February 2020

	20 March 2020
Date(s) of receipt of responses from MAH:	07 February 2020 20 March 2020
Date of final version of report:	07 April 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Alexion Pharma UK 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.

Alexion Pharma UK is an affiliate of Alexion Europe SAS (hereafter 'Alexion') which is owned by the global organisation Alexion Pharmaceuticals, Inc. with headquarters in Boston, US. Global pharmacovigilance activities are carried out by the global drug safety department based at Alexion's offices in Boston and New Haven in the US with the support of local drug safety units at affiliate offices.

ICSR entry, processing and submission to competent authorities and aggregate reporting writing were subcontracted to PPD. Global medical information services were provided by ProPharma Group.

Alexion Europe SAS is the MAH of the following four centrally authorised biological medicines, three of which were designated orphan medicines at the time of the inspection:

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[redacted] was authorised on 20 June 2007 for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome in adult and paediatric patients, and for the treatment of refractory generalized myasthenia gravis and in neuromyelitis optica spectrum disorder in adults.

[redacted] was authorised on 28 August 2015 for the long-term enzyme replacement therapy in patients with paediatric onset hypophosphatasia to treat the bone manifestations of the disease.

[redacted] was authorised on 28 August 2015 for long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase deficiency.

[redacted] was authorised on 02 July 2019 for the treatment of paroxysmal nocturnal haemoglobinuria in adults. At the time of the inspection, the product was not yet launched in the UK as the additional risk minimisation measures, consisting of physician and patient educational materials, the controlled distribution system and annual vaccination reminders, were yet to be approved by the MHRA.

At the time of the inspection, the PSMF was located at Alexion's offices in France, therefore the French National Agency for Medicines and Health Products Safety (ANSM) was the Supervisory Authority responsible for conducting pharmacovigilance inspections on behalf of the EMA.

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems and was performed at Alexion's offices in Uxbridge, Greater London. Personnel from the UK and US offices attended the Uxbridge site in order to participate in the inspection. In addition, staff based at the Alexion US offices participated in the inspection via teleconference.

The inspection was performed using interviews and document review (including outputs from the global safety database and listings of medical information enquiries and product complaints). The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

Maintenance of the reference safety information and conduct and reporting of PASS were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

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B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 02 July 2019) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection. The detail of these requests is contained within document request sheet A.

B.4 Conduct of the inspection

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

The inspection was not completed during the onsite days (16 – 19 September 2019) and an interim closing meeting was held at Alexion's UK office, Uxbridge on 19 September 2019 to summarise the inspection status and to provide preliminary feedback regarding the inspection findings. The inspection was concluded via office-based document review and a formal closing meeting was conducted via teleconference on 07 October 2019.

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

SECTION C: INSPECTION FINDINGS

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

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

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- The EU QPPV changed from [redacted] in July 2017; and from [redacted] in March 2018.
- Outsourced activities for ICSR management and aggregate report writing was transferred from Inventive Health Clinical to PPD in December 2017.
- At the time of the inspection, the MAH was in the process of implementing a validated tracking system (Orbit®) to track RMP submissions and approvals, aRMM submissions and approvals, and the distribution of educational materials locally. The system went live in August 2019 and initial data entry was due to be completed by the end of October 2019, including a quality check step. At the time of the inspection Orbit was not yet in use in the UK.
- The MAH had submitted proposals for the [redacted] aRMM (physician and patient educational materials, controlled distribution system, annual vaccination reminders) to MHRA for approval in July 2019. At the time of the inspection, these were not yet agreed and the MAH had been asked by the MHRA assessor to implement a number of changes to the proposed materials and processes.

  As the additional risk minimisation measures for [redacted] were based on the existing ones for [redacted] the assessor recommended that the changes for [redacted] would also be considered for the Soliris additional risk minimisation measures.

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 Signal Management

Requirements:

Commission Implementing Regulation (EU) No 520/2012, Article 12(1) "*Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents […].*"

GVP Module IX – Signal management (Rev 1)
IX.B.2. Signal detection
"*Data from all appropriate sources should be considered […].*"

IX.B.3. Evaluation during signal validation and further assessment
"*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), […]
− additional cases reported with related terms (e.g. other MedDRA terms indicating clinical complications or different stages of the same reaction); […]"

IX.B.5. Quality requirements
"*Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities.*"

"*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.*" (emphasis added)

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).*"

"*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. Implementation of strengthened processes for routine pharmacovigilance will facilitate earlier detection of new risks and changes in product safety or quality over time.*"

MAHs are obliged to ensure that information on the benefits and risks of their products is evaluated on an ongoing basis and appropriate action is taken in response to new information that impacts on the benefit-risk balance.

The following findings were noted in relation to signal management:

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Finding MA.1 a)

As the Alexion product portfolio consisted of four biological products, the requirements laid out in GVP 'product- or population-specific considerations II for biological medicinal products' applied. This included the requirements that signal detection processes for biological products should be sensitive to detect quality differences between batches, particularly following manufacturing changes and that all signals should be evaluated in the context of batch-specific exposure data. Alexion had failed to fulfil these requirements, specifically:

i. The records of signal detection activities for [redacted] that were reviewed for the period of 01 January to 31 March 2019 did not include any mechanism to monitor denominator data (exposure information) and data of suspected adverse reactions to support the detection of any apparent changes in suspected adverse reaction reporting rates or trends between batches of the same product, such as batch trending or the analysis of denominator data alongside reports of suspected adverse reactions.

   The only reference to batch analysis was within the quarterly "Product complaint AEs" report, in which lack of efficacy reports for that interval only were reviewed to identify whether there was an association with a specific batch.

   GVP PII, section P.II.B.4. *Signal management* states that "*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).*"

   It is acknowledged that separate to signal detection processes, an analysis of product quality complaint trends, including those associated with an adverse event or lack of efficacy, was conducted monthly by the quality department. Complaint data for a 12-month period was normalised by product by dividing the number of complaints per month by distribution volume per month, to identify any trends or spikes in reports. However, the data was not normalised by batch, and only after investigation was triggered through a spike or trend in reporting, was batch investigated as a potential cause.

ii. The Signal Assessment Report completed for the validated signal concerning [redacted] and iron overload did not include any evidence that this signal was evaluated in the context of batch-specific exposure data. The signal was eventually refuted.

iii. SOP [redacted] *Signal Surveillance* (v8.0, date effective 03 June 2019) did not reflect the specific requirements regarding signal management in relation to biologicals as stated in GVP PII.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

Preventative Action(s)
[redacted]

[redacted]

Finding	MA.1 b)

Not all data in the safety database was included in the monthly signal detection report interval tabulation.

Cases in the safety database were identified by inspectors that contained events for which no event received date was coded. New events received during the interval period from case follow-up, for which this Event Received Date field was blank, would only be included in the interval tabulation if the initial received date was also in the interval period. Instead, these events would show in the cumulative tabulations of the signal detection report but would be indistinguishable from the rest of the cumulative data and never be considered during monthly signal detection activities.

Beginning with version 2 (dated 15 October 2014), the Alexion Argus Data Entry Conventions Manual instructed that the Event Receipt Date field be populated. In addition, on 16 January 2016, an Argus Safety (soft) validation check was deployed as a further prompt to ensure Event Receipt Date was populated during case processing.

In a post-inspection investigation provided on 29 October 2019, the MAH confirmed that a total of 185 events in 118 cases were identified with missing event receipt date post deployment of the soft validation check in the Argus database for the event receipt date field on 16 January 2016. The investigation report is included in Appendix III of the inspection report.

[redacted]

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[redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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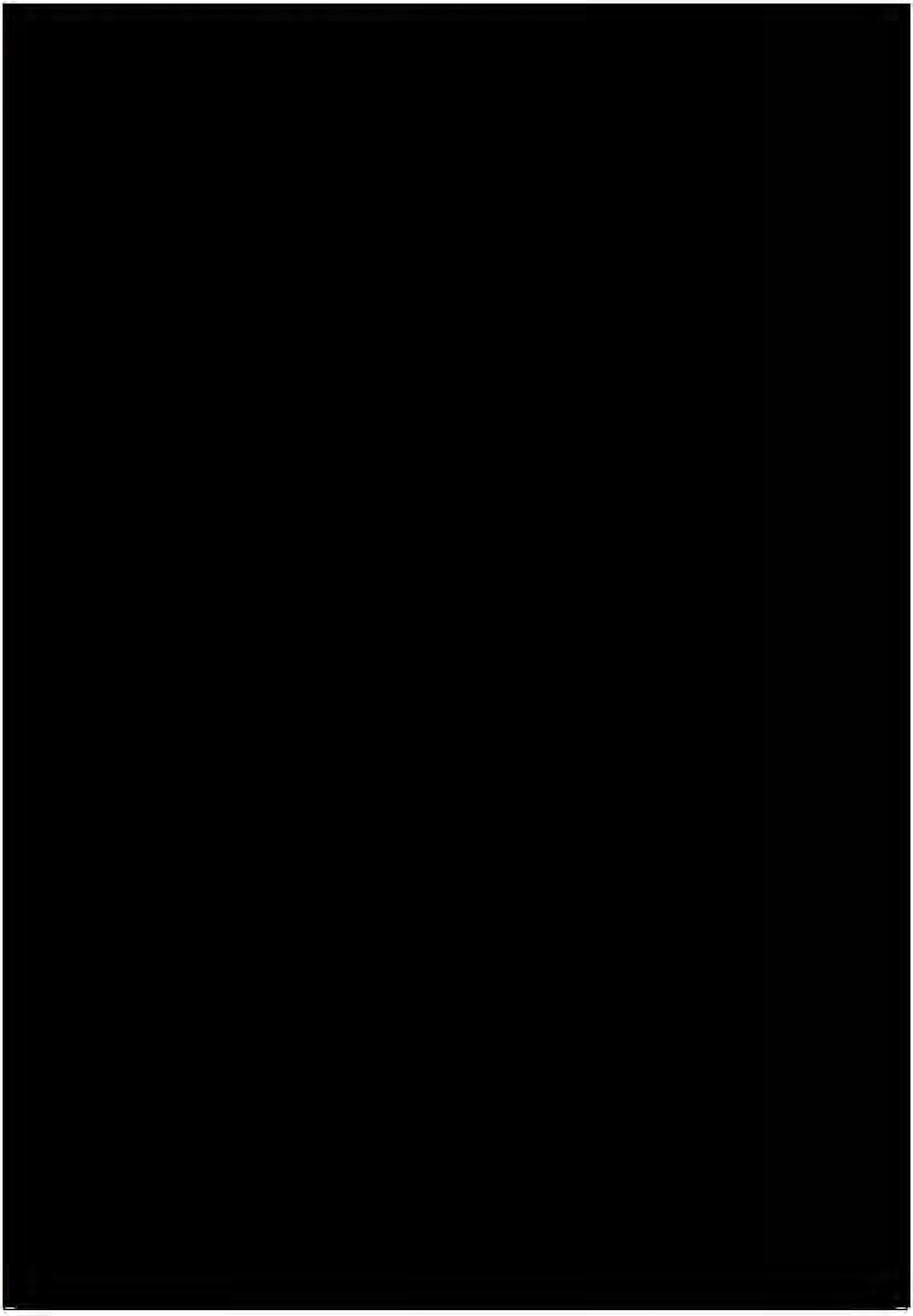

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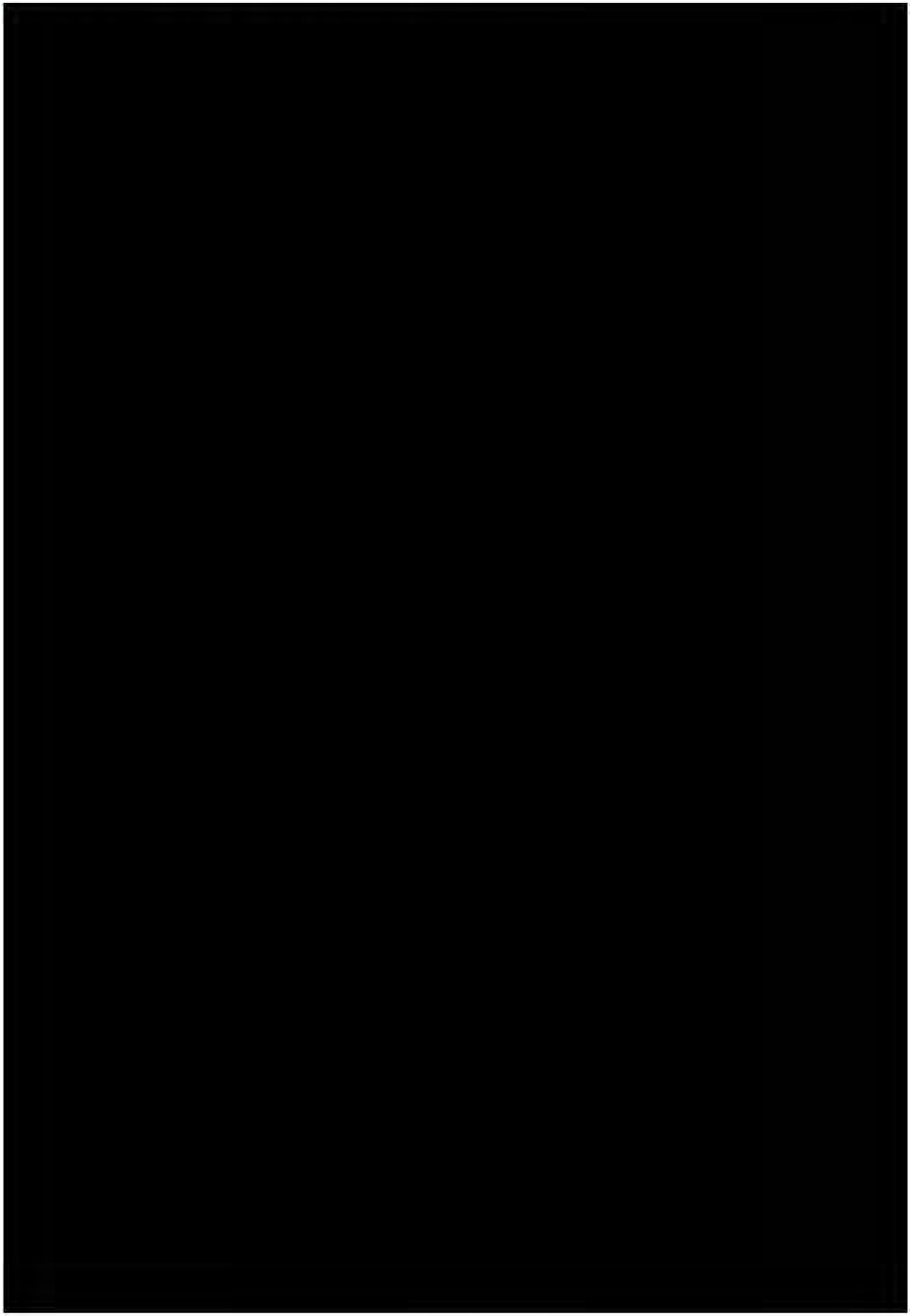

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[redacted]

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

Finding MA.1 c)
For the potential signal of [redacted] and atrial fibrillation, not all available information was used within the signal validation process. As per [redacted] *Signal Review Meeting template* [redacted], date effective 01 November 2018) the signal validation process used four criteria of which three were required to validate a signal. One criterion was strength of association defined as "cases of the same or similar event seen before". To assess the strength of association, the MAH conducted a search in the safety database using the MedDRA High Level Term (HLT) 'Supraventricular arrhythmias' for the report

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period in which the signal was identified (May 2019). A search of the database for events reported within the HLT prior to May 2019 was not conducted.

A review of AE reports received since January 2017 by inspectors identified a report of supraventricular tachycardia with [redacted]); however, this report was not considered as part of the signal validation. It was also noted that the Signal Review Meeting minutes (dated 18 July 2019) recording the decision to not validate the above signal did not document the evidence presented to make this decision (i.e. search criteria and parameters).

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 d)

The methodology for review of Signalling reports form Argus and for review of EVDAS reports was not documented, including the thresholds used to identify potential signals and

the supporting rationale. As such, there was no guidance for PV safety scientists, who reviewed the various signal detection inputs on how to identify potential signals requiring further investigation and processing to signal validation.

For the internal data review, the MAH verbally described qualitative processes during the inspection. For example, in relation to the 'Signalling reports from Argus', it was stated that fatal cases, events occurring for the first time, an increased frequency of events, and any "unusual events" unexpected to occur in the patient population were reviewed in greater detail.

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For [redacted] the MAH verbally stated that signals of disproportionate reporting were highlighted for detailed review. The user guide and training materials, described by the MAH as tools used to aid signal identification, only comprised of the guidance published by the EMA on possible methods for signal detection.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 e)

The deadline for evaluating the validated signal of [redacted] and iron overload was missed by almost three weeks without an approved extension. The signal was identified on 29 April 2019 and was assigned a routine priority of 90 days to complete signal evaluation, i.e. by 28 July 2019. Signal evaluation was not completed by this date and the deadline was only extended to 12 September 2019 at the Safety Management Team Meeting on 15 August 2019. Signal evaluation was completed on 12 September 2019 and the signal was refuted.

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 MA.1 f)

As per GVP Module IX – Signal management (Rev 1), section *IX.B.5. Quality requirements* "Any signal management system should be clearly documented to ensure […] that the roles, responsibilities and required tasks are clear and standardised, […]" (emphasis added). The MAH did not comply with this requirement as signal detection activities for [redacted] were not conducted in line with the product-specific signal detection plans (SDPs). Signal detection activities were reviewed for the period 01 January 2019 – 31 March 2019 and the following deficiencies were identified:

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[redacted] dated 19 December 2018) and [redacted] dated 17 December 2018)

i. No FDA AERS Signal report was produced for the reviewed period even though Table 1 *Sources and Review Plan for Routine Signal Detection* of the SDP for either product stated that the AERS Signal report would be reviewed quarterly. The MAH stated that the reason for exemption of this report was the expiration of the service provider contract in mid-May 2019 that enabled access to the data. It should be noted that the contract expired after the specified review period.

[redacted] dated 19 December 2018)

ii. Table 2 *Risk Monitoring of the SDP* stated that the important identified risk of severe thrombotic microangiopathy complications due to drug discontinuation in aHUS patients would be reviewed biannually. In practice this risk was only reviewed annually in line with the aHUS Registry interim report data analysis.

iii. The EVDAS Signalling report was not produced and reviewed in March 2019 even though this was required as per Table 1 of the SDP, and there had been no retrospective review of this period.

It is recognised that [redacted] was not on the list of active substances involved in the pilot on signal detection in EudraVigilance.

[redacted] dated 17 December 2018)

iv. Table 2 *Risk Monitoring of the SDP* detailed the important identified risks as included in the EU RMP (e.g. medication errors, immunogenicity and injection associated reactions including hypersensitivity) that would be reviewed quarterly for [redacted] The MAH stated that for Q1 2019 the risks outlined in Table 2 were reviewed utilising the quarterly signal detection output from Argus. However, there were no records showing evidence of specific reviews for the important identified risks.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.1 g)

The status of the signal of [redacted] and serious cutaneous adverse reactions (SCARs) was not correctly documented in the signal trackers.

Alexion's signal surveillance process was updated on 01 November 2018 to incorporate improvements and streamline the process. At the time of the inspection, the current signal tracker in use was an interim solution while a new signal detection tool was being developed (with a target launch date of Q1 2020). The interim tracker contained signals identified for all approved Alexion products since 01 January 2018. Prior to November 2018, signals were tracked in Excel format per product.

The signal of [redacted] and SCARs was documented as ongoing on the signal trackers utilised prior to November 2018 and had not been transferred to the interim signal tracker in current use. Evidence was provided confirming the signal was closed in April 2017; however, this information was not reflected on any of the signal trackers.

This finding has been graded as minor due to the isolated nature of the issue but is grouped within the major finding for signal management.

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Root Cause Analysis	
[redacted]	
Further Assessment	
[redacted]	
Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MA.2 Additional Risk Minimisation Measures

Requirements:

Commission Implementing Regulation (EU) No 520/2012, Article 12(1) "*Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents […].*"

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)
XVI.B.2.1.1. Educational tools
"*Educational tools should refer the reader to the SmPC and the package leaflet.*"

XVI.C.2. Roles and responsibilities of the marketing authorisation holder or applicant in the EU
"*The methods for dissemination and the target audience in each Member State are determined at national level by the respective competent authority of the Member State.*"

"*Marketing authorisation applicants/holders in the EU are responsible for ensuring compliance with the conditions of the marketing authorisation for their products wherever they are used within the EU.*"

GVP Module XVI Addendum I – Educational materials
XVI. Add.I.2 Principles for educational materials
"*The date of approval by the competent authority the Member State should be included in the educational material, as reference for healthcare professionals and/or patients.*"

XVI. Add I.3. Submission of educational materials
"*If no other national requirements apply, the draft educational material should be submitted to the competent authorities of Member States as follows: […]*

- *a detailed implementation plan for the educational material with the following information:*
  - target population(s);
  - dissemination method (e.g. paper, e-mail, via social media, learned societies and/or patient associations, publication on websites);
  - time point when dissemination is anticipated to start and frequency of further disseminations; […]."

The marketing authorisations of all of Alexion's products were attached to conditions involving additional risk minimisation measures.

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As treatment with [redacted] increases the risk of severe infection and sepsis, especially with Neisseria meningitidis and other Neisseria species, the additional risk minimisation measures for this product consisted of a controlled distribution system, educational materials and annual vaccination reminders. The measures were in place to ensure that:

1. *All healthcare practitioners who may prescribe* [redacted] *receive the appropriate educational material.*

2. *All patients being treated with* [redacted] *receive a patient safety card.*

3. *Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.*

4. *Vaccination reminders are sent to the prescribers.*

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For [redacted] educational materials consisting of a guide for healthcare professionals were required to encourage healthcare professionals to enrol patients in the prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase (LAL) Deficiency to monitor for efficacy and safety of [redacted] (LAL Deficiency Registry). The registry evaluated the product's safety, particularly in relation to hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies development impacting the response to the drug.

For [redacted] educational materials consisting of self-injection guide for patients or injection guide for parents or caregivers with infant patients were required to provide instruction for proper administration techniques to address the risks of medication errors and injection site reactions.

Finding MA.2 a)

The MAH supplied [redacted] to the externally sponsored [redacted] trial ([redacted]) and as part of the protocol alternative risk minimisation measures for the prevention of meningococcal disease in trial patients were agreed between the study sponsor and the MHRA. The protocol ([redacted], dated 20 April 2017) described Alexion's responsibilities in relation to the controlled supply of [redacted] in *Appendix 2: Proposed Alternative Risk Minimisation Measures* as "Alexion to distribute [redacted] of an agreed quantity to each trial site along with educational risk minimisation materials (for all participants whether receiving [redacted] or placebo) only upon receipt of confirmation from the trial sponsor that all trial approvals (MHRA approval, REC approval, HRA approval) are in place for that site."

The MAH did not adhere to the conditions of the alternative aRMMs as they provided [redacted] to 11 trial sites up to four months before confirmation of the MHRA approval of the trial protocol was received from the trial coordinator on 15 November 2017.

It should also be noted that the MAH was not able to provide any records demonstrating the date they had first received confirmation of the REC and HRA approvals from the trial coordinator.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.2 b)

Patient information such as date of birth and date of meningitis vaccination from the Certificate of Vaccination (CoV) was entered in the SAP database for all patients who were prescribed [redacted] as a record for ensuring the controlled distribution system. Inconsistencies were identified between the data in SAP and the information on the CoV.

As an example, vaccination dates were entered incorrectly entered for patients without confirmation of vaccination, e.g. patient [redacted] and patient [redacted], for which the CoV only stated that the patients had received prophylactic antibiotics.

Additionally, there was an example of an incorrect vaccination date being recorded in the system. For patient [redacted] the SAP patient record incorrectly stated that the patient was

vaccinated on 29 May 1979 whereas the CoV stated that the patient was vaccinated on 07 September 2019.

Alexion is reminded of the requirement in [redacted] that "Quality assurance mechanisms should ensure that the distribution systems in place are fit for purpose and auditable."

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 c)

The following deficiencies were identified in relation to the submission of updated educational materials for [redacted] to MHRA for approval.

i. The UK educational materials for [redacted] were updated and submitted to MHRA for approval on 21 April 2017, 19 February 2018 and 07 December 2018 following approval of safety variations [redacted] respectively. In these instances, the submission e-mail did not include any information on the target population, dissemination method, and the time point when dissemination was anticipated to start and the frequency of further disseminations.

ii. The UK educational materials for [redacted] were updated and submitted to MHRA for approval on 25 May 2017 following approval of safety variation [redacted] The submission

e-mail did not include any information on the target population, dissemination method, and the time point when dissemination was anticipated to start and the frequency of further disseminations.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

Finding MA.2 d)

The following deficiencies were identified in relation to the content of hard-copy educational materials for [redacted]

i. Hard copies of the updated UK [redacted] educational materials (dated November 2018) were re-distributed to existing prescribers from 17 to 24 May 2019 but did not contain the SmPC as required per Annex IID of the marketing authorisation. The MAH verbally stated that a link to the SmPC on the eMC would be included in the cover letter accompanying the hard copy materials; however, in this instance the cover letter (dated 30 April 2019) did not include a link to the SmPC.

ii. The hard copy educational package for [redacted] dated July 2017) did not include the PIL as required per Annex IID of the marketing authorisation. The accompanying cover letter also did not include a link to the PIL on the eMC. It is acknowledged that the self-injection guide included link to the patient website [redacted]

iii. The date of the updated UK [redacted] educational materials (November 2018) did not match the MHRA approval date (20 December 2018).

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 e)
The following deficiencies were identified in relation to the distribution of educational materials to healthcare professionals. i. There were no records demonstrating that the MAH adhered to the distribution plan for

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the [redacted] educational materials. The plan was agreed with the MHRA on 17 December 2015 and stated that Alexion would proactively send the materials to 27 "key Healthcare Professionals in [9 specialist Lysosomal Storage Disorder specialist centres across the UK]".

It was seen that five of these HCPs had received the materials subsequently in 2016 and 2017 after prescribing [redacted] for their patients. For the remaining 22 HCPs specified in the distribution plan, the MAH was unable to provide any records showing that they had ever received the materials. It is acknowledged that none of these HCPs had prescribed [redacted] yet.

In addition, the following minor discrepancies were seen. These have been grouped within the major finding.

ii. There was a delay of two months in distributing the updated [redacted] education materials (dated November 2018) to existing prescribers. MHRA approval of the materials was received on 20 December 2018 and the distribution should have taken place by the end of March 2019; however, it only took place from 17 to 24 May 2019.

[redacted] *Submission to Competent Authorities and Distribution of Educational Materials to Healthcare professionals and Patients* [redacted], date effective 01 November 2018), section 4.5.4 stated "The Regulatory Affairs Regional or Country Lead must provide local updated, approved [educational materials] to HCPs/ patients within 90 days of receipt of approval from the NCA [...]."

iii. There was one example where a patient's physician had not received the updated [redacted] educational materials (dated November 2018) following MHRA approval in December 2018. The patient was under the shared care of two physicians at Leeds General Infirmary; however, only one set of the materials was sent to one of the physicians on 20 May 2019.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.2 f)

The MAH did not adhere to their own procedure to ensure that only the current educational materials were in circulation:

i. When updated educational materials for [redacted] (dated November 2018) and [redacted] (dated July 2017) were re-distributed to existing prescribers, the accompanying cover letter did not include any instructions on the destruction of superseded materials still held by HCPs.

[redacted] *Approval and Distribution of Educational Materials to HCPs* [redacted], date effective 20 March 2017 and [redacted] date effective 10 December 2018) stated in section 4.4.3 "Recipients will be advised to destroy all previous versions of the educational materials in their possession".

ii. There were no records demonstrating that the vendor DICE, responsible for printing educational materials and their interim storage, had been notified to destroy any remaining stock of the superseded version of [redacted] educational materials after MHRA approval of the updated version was received in December 2018.

[redacted] *Approval and Distribution of Educational Materials to HCPs* [redacted], date effective 10 December 2018) stated in section 4.5.3 "All previous version of the materials available in the APUK office, or in a location within APUK's control, will be destroyed, […]".

This finding has been graded as minor but has been grouped within the major finding for additional risk minimisation measures.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

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

MA.3 Quality Management System

Requirements:

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.6. Responsibilities for the quality system within an organisation
"*For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for: […]*

- *identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary*".

GVP Module IV - Pharmacovigilance audits (Rev 1)
IV.B.2.4. Actions based on audit outcomes and follow-up of audits
"*The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.*

Upper management and those charged with governance, should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to upper management."

The following findings were noted in relation to the effective resolution of CAPA in a timely manner:

Finding MA.3 a)

There was a delay of four years in implementing effective corrective and preventative actions to address non-compliance identified through an internal audit concerning Alexion's compassionate use programmes to ensure that all safety-relevant information was forwarded to the pharmacovigilance team. Repeat findings were reported for deficiencies in this area in 2015, 2016, 2017, and 2018.

An internal audit of the global compassionate use and medical information functions, conducted by Alexion in 2015, identified issues in the management, recording, assessment and reporting of relevant safety data from the six-monthly follow-up reviews that were being conducted with participating physicians. The corrective actions included the standardisation of the six-monthly follow-up process, development of status reports and the transfer of all Excel data files into "Smart Sheet" format.

A further audit conducted in June 2016 identified continued issues in relation to the completeness and consistency of safety relevant data collected from the Global Access to Medicine (GATM) programme. A new database was planned to support the end-to-end process so that product supply to patients was aligned with the approved treatment length and current treatment status, but it was not deployed due to financial and personnel constraints.

In June 2017, a reconciliation activity was completed as part of the corrective actions from the audit in 2016. During the reconciliation 32 reports of death were identified that were previously unreported to global pharmacovigilance.

The most recent audit was conducted from 17 December 2018 to 29 January 2019 to verify the pharmacovigilance event reporting compliance from both compassionate use programmes. The audit resulted in a critical finding as 66 adverse event reports in correspondences originating from the compassionate use programmes and which had not been reported to global pharmacovigilance were identified.

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Alexion operated two separate compassionate use programmes since 2008. The GATM programme enabled access to Alexion's products to patients outside of the US. Since its start approximately [redacted] patients have been enrolled in the programme of which [redacted] patients were active at the time of inspection. The Alexion Access Foundation provided access to approved products for patients within the United States.

At the time of the inspection, a remediation plan had been drafted and had been put into action since 07 May 2019. The first phase of remediation involved the collation of all medical documents per patient which would then be reviewed for all relevant safety information in phase 2 of the project. Where applicable the information would then be sent to PPD for processing and submission. Phase 2 was due for completion on 31 October 2019.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

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[redacted]

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

Finding MA.3 b)

The MAH failed to implement effective corrective and preventative actions after they identified in September 2018 that they had failed to send the annual vaccination reminder to prescribers of [redacted] in 2017 (CAPA number [redacted]

i. As the corrective action, the vaccination reminder was sent by Alexion via e-mail on 13 November 2018 to all prescribers and pharmacists who had prescribed or dispensed the product in 2017 and 2018. However, there were five UK HCPs at the following institutions to whom the annual vaccination reminder was not sent, even though they had placed [redacted] orders for patients in 2017:

- Evelina London Children's Hospital
- Great Ormond Street Hospital
- Alder Hey Children's Hospital NHS Foundation Trust
- Southampton Children's Hospital
- St James's Hospital

ii. On 18 November 2018, Alexion sent the routine annual vaccination reminders via e-mail to all prescribers and pharmacists who had prescribed or dispensed the product in 2018. However, there were five UK HCPs at the following institutions to whom the annual vaccination reminder was not sent by Alexion even though they had placed [redacted] orders for patients in prior to November 2018:

- University College London Hospital Cancer Centre
- Great North Children's Hospital
- Northern General Hospital
- Freemans Hospital
- Guy's Hospital

The procedure effective at the time, [redacted] *Vaccination and Prophylactic Antibiotics Control within* [redacted] *Distribution* [redacted], date effective 18 July 2018), stated in section 4.4.2 "On an annual basis, the APC RA Lead reminds prescribers/ pharmacists who signed CoV to check if re-vaccination is needed for his her patients on [redacted]. Reminder letters and mailings to HCPS are maintained by the APC RA Lead in an accessible repository. […] The annual reminder letters and mails are sent to pharmacists/ HCPs who have signed the CoV of patient(s) for whom at least one order has been received within the last year."

Root Cause Analysis

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[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

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

Finding MA.3 c)

There were examples of CAPA from audits and inspections which had passed their due date but for which no further extension had been agreed at the time of inspection.

i. [redacted] from the [redacted] inspection in January 2018 related to the implementation of a centralised tracking tool to measure risk management plan and aRMM implementation. The CAPA due date was 30 June 2019; however, it was only closed on 08 August 2019 and no Interim Status Report was completed to extend the CAPA due date as required per Alexion procedure [redacted]

ii. [redacted] from the [redacted] audit conducted from April to June 2018 (audit number [redacted] required an update to the SDEA between Alexion and [redacted] The original due date was 31 March 2019 and an Interim Status report was approved on 07 April 2019 to extend the CAPA due date to 30 June 2019. However, the action was only completed on 09 September 2019 and no further extension was agreed beyond 30 June 2019 in line with procedure [redacted] It is acknowledged that the senior leadership team was informed of the overdue CAPA on 16 July 2019 as part of the Q2 2019 Quality Management Review.

[redacted] *Enterprise Action Management* [redacted] date effective 10 December 2018), section 5.5 stated "An Interim Status Report (ISR) must be documented where an Action or Effectiveness Check cannot be completed by the approved due date. […] The ISR will include: 1. ISR Due Date. 2. Extension Details […]".

Root Cause Analysis

[redacted]

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[redacted]

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

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

MA.4 Post-authorisation Safety Studies

Requirements:

Commission Implementing Regulation (EU) No 520/2012, Article 36(3) "*The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information [...].*"

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[redacted] was authorised under exceptional circumstances and a condition of the marketing authorisation for the MAH was to set up an observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with [redacted] (category 2 PASS, [redacted] Annual re-assessment reports had to be submitted to the EMA which also included information on the distribution of educational materials to enrolled patients via their HCPs. At the time of the inspection 98 UK patients were enrolled in the registry, of which 16 had ever received treatment with [redacted]

Finding MA.4 a)

The eCRFs and annual reassessment reports of this PASS were reviewed in relation to the information provided on the [redacted] educational materials. The following deficiencies were identified.

i. The eCRF for patient [redacted] (enrolment date 20 November 2017) did not include the required information on whether the patient/ caregiver had received the educational materials from the treating physician. Data entry queries were raised on 27 November 2018, 13 December 2018 and 22 January 2019 but were subsequently closed without a response from the study site. It was noted that for the patient's third observational visit on 12 June 2019, the HCP had entered "no" in response to "Did the patient/care-giver receive educational materials (injection guide)?, but in response to the question "If yes, how were the materials accesses" replied "already received".

   Accurate information in the eCRF was important as the data on the provision of the educational materials was extracted for inclusion in the annual reassessment reports. Furthermore, the EU RMP [redacted], date of final sign off 09 May 2019) for [redacted] stated in section [redacted] *Additional risk minimisation measures* that "The MAH will track and assess the receipt of educational materials through the HPP registry."

ii. Inaccurate information was reported in the 2018 annual reassessment report (DLP 03 July 2018), section 10.2.10. *Access to Educational Materials: Injection Guide*:

   - The section incorrectly stated that six UK patients were enrolled in the registry and had received treatment with [redacted] however, information provided during the inspection showed that eight patients were enrolled and had received [redacted] at the time of the data lock point.

   - The section stated that that none of the six enrolled patients at the time had received the educational materials. However, upon review of the eCRF for patient [redacted] (enrolment date 07 June 2017), it was identified that the patient had received the Strensiq educational materials during observation visit 1 on 20 November 2017.

Root Cause Analysis

[redacted]

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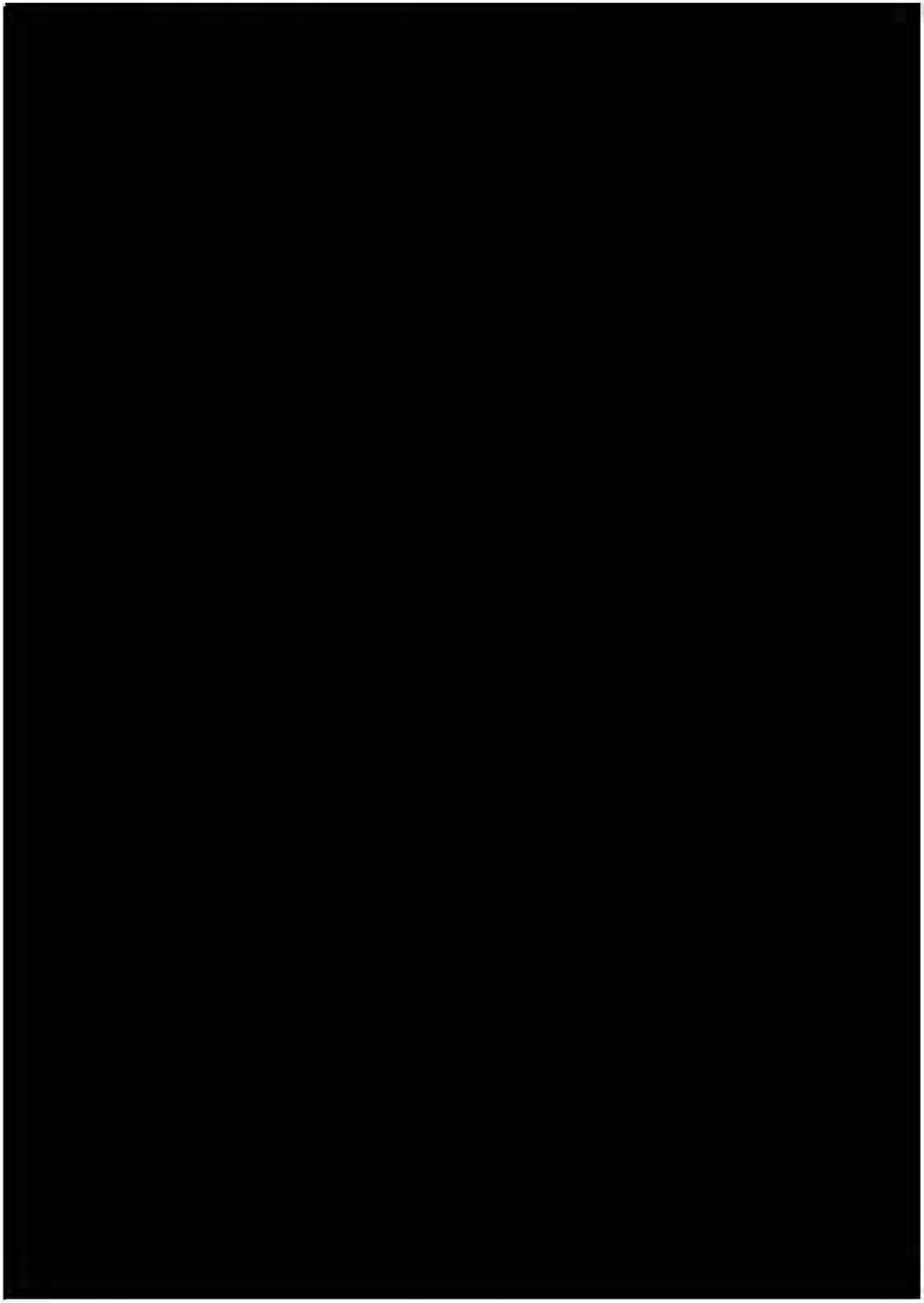

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[redacted]

Further Assessment

[redacted]

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Corrective Action(s)
[redacted]
[redacted]
Preventative Action(s)
[redacted]

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[redacted]

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

Finding MA.4 b)

The eCRF for patient [redacted] enrolment date 06 September 2017) showed an open data entry query from 09 August 2018 relating to the protocol version for which informed consent was obtained but that had not yet been resolved at the time of inspection.

The query related to the protocol version to which the enrolled patient had consented and asked that the study site amended this information. The eCRF stated that consent was obtained for protocol version 1.1; however, the Patient Informed Consent Form [redacted] was related to protocol [redacted] and the protocol version in the eCRF should have been amended to reflect this.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

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

C.4.3 Minor findings

MI.1 Management and Reporting of Adverse Reactions

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Finding MI.1 a)
There was one case which had been incorrectly coded as non-serious even though it contained a serious event. [redacted] was a solicited case from the US initially received on 16 March 2018 for [redacted] reporting the serious event of hospitalisation for a hip replacement. The case processing vendor incorrectly added follow-up information to the case on 28 September 2018, which resulted in the case seriousness field being overwritten from serious to non-serious. At the time of the inspection, the case had not been corrected yet.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]

Finding MI.1 b)
There was no procedural documentation defining the timeline for updating Argus once a decision had been taken to update the reference safety information used for listedness assessment. For authorised products, the list of expected events was based on the EU SmPC and was defined in product-specific datasheets in Argus for automatic assessment of listedness in the event assessment tab. This finding has been graded as minor, as no examples were identified where out-of-date reference safety information was used for case assessment in the safety database.
Root Cause Analysis
[redacted]

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Further Assessment
[redacted]

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

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

Finding MI.1 c)
From a listing of all action items opened since 2017, it was noted that action items relating to follow-up for further information had not been completed for approximately 100 cases. There were also approximately 500 action items related to follow-up that were completed after their assigned due date. The Alexion *Argus Data Entry Convention Manual* [redacted] dated 15 September 2019) stated in Appendix F *ICSR Follow-Up Query Guideline*, section 10. Query Closure "When a follow up is received and queries have been answered the user should close the queries in Argus". The manual also instructed that if no response was received to a request for follow-up, the relevant action item would be escalated to Alexion for resolution.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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[redacted]

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

MI.2 Collection and Collation of Safety Information

Section 43

Finding MI.2

The MAH did not adhere to the oversight mechanisms put in place to ensure that all safety information was sent from homecare providers in the UK to Alexion:

i. The reconciliation between [redacted] and Alexion for Q2 2019 was only completed on 16 September 2019 and there were no records showing when reconciliation was initiated.

Schedule 7 *Safety Agreement* (last signed 09 April 2018) to the [redacted] (last signed 09 April 2019) stated in section 8.5 Reconciliation of Safety Information "Vendor will provide a listing of cases submitted to Alexion Global Pharmacovigilance at least monthly […]."

In addition, [redacted] *Patient Support Programs - Initiation, Management, Oversight, and Termination* [redacted] date effective 09 February 2018) stated in *Appendix 1: Pharmacovigilance Patient Support Program Oversight Activities* that "Any errors found during reconciliation are to be communicated to the vendor and rectified within the week […]."

ii. There were no minutes documenting the oversight meeting with [redacted] that took place on 21 March 2019.

[redacted] *Patient Support Programs - Initiation, Management, Oversight, and Termination* [redacted] date effective 09 February 2018) stated in *Appendix 1: Pharmacovigilance Patient Support Program Oversight Activities* that teleconferences with the service provider should be recorded in minutes and the file stored.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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Preventative Action(s)	
Deliverable(s)	**Due Date(s)**

MI.3 Routine Risk Minimisation Measures

Section 43

Finding MI.3

The Homecare providers [redacted] not informed of the update to the [redacted] SmPC following approval of variation II/0103 on 20 September 2018 which involved updates to SmPC section 4.4, 4.5 and 4.8 describing reports of serious infections with Neisseria species (other than Neisseria meningitidis), including disseminated gonococcal infections, the theoretical potential for drug-drug interaction between [redacted] and intravenous human immunoglobulin [redacted] and clarifying sepsis as the most common presentation of Neisseria meningococcal infections.

APUK SOP *Communicating Latest Product Label information in Alexion Pharma UK* [redacted] effective from 01 May 2018 to 16 January 2019) stated in section 4.4.4 "APUK will also proactively inform the external service providers who are affected by these changes, e.g. Medical Information, Homecare Providers, as appropriate."

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

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.

Major finding MA.5 was downgraded to minor finding MI.3 following submission of additional supporting information by the MAH after the initial inspection report was issued. An explanatory note by the lead inspector was also added to the finding.

D.2 Recommendations

At the time of the inspection, significant changes were being introduced in relation to the system for tracking and implementing RMP commitments, including additional risk minimisation measures. As major findings were reported in this area, the Lead Inspector has recommended that the next MHRA inspection is performed within the next 12 to 18 months from the date of this inspection.

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.
- Commission Implementing Regulation (EU) No 198/2013.
- 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/PhVWP/235910/2005: “Guideline on conduct of pharmacovigilance for medicines used by the paediatric population”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 31187/19028368-0001	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Alexion Europe SAS	**DATE**	16 September 2019
LOCATION	3 Furzeground Way, Stockley Park, Uxbridge, UB11 1EZ	**START TIME**	09:00 arrival for a 09:30 start

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system and the quality system. The presentation may also include information on any relevant ongoing remediation work in the pharmacovigilance system. *(approx. 20 minutes)*	[redacted]	[redacted]
Document Review		
LUNCH		

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ICSR management, including but not limited to • Data entry, coding assessments and submission to EudraVigilance • Follow-up activities	[redacted]	[redacted]
Collection of safety information, including but not limited to • Medical enquiries • Product quality complaints • UK Patient Support Programmes	[redacted]	[redacted]
[redacted]		

MHRA INSPECTION NUMBER	Insp GPvP 31187/19028368-0001	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Alexion Europe SAS	**DATE**	17 September 2019
LOCATION	3 Furzeground Way, Stockley Park, Uxbridge, UB11 1EZ	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Additional risk minimisation measures, including but not limited to • Implementation and maintenance of UK educational materials • Controlled distribution in the UK	[redacted]	[redacted]
LUNCH		
Signal detection and management	[redacted]	[redacted]

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MHRA INSPECTION NUMBER	Insp GPvP 31187/19028368-0001	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Alexion Europe SAS	**DATE**	18 September 2019
LOCATION	3 Furzeground Way, Stockley Park, Uxbridge, UB11 1EZ	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Integrity of data in aggregate reports, including but not limited to • PSURs • Annual re-assessment reports • Interim and final study reports	[redacted]	[redacted]
LUNCH		
Document Review		

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MHRA INSPECTION NUMBER	Insp GPvP 31187/19028368-0001	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Alexion Europe SAS	**DATE**	19 September 2019
LOCATION	3 Furzeground Way, Stockley Park, Uxbridge, UB11 1EZ	**START TIME**	09:00

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Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Review of [redacted] PASS eCRF	[redacted]	[redacted]
Document review and ad-hoc questions	-	As required
LUNCH		
Closing meeting	[redacted]	All welcome

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[redacted]