Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE
INSPECTION REPORT

Pharmacovigilance System Name:	EUSA Pharma (UK) Ltd
MHRA Inspection Number:	Insp GPvP 44185/11625545-0004

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

Table of Contents

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DCP	Decentralised Procedure
DEC	Drug Event Combination
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study

PBRER	Periodic Benefit Risk Evaluation Report
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection
System(s) inspected:	EUSA Pharma (UK) Ltd, [redacted]
Site(s) of inspection:	EUSA Pharma, Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ
Main site contact:	[redacted] Address: Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ [redacted] Address: Aasmund Vinjes vei 32, 0373 Oslo, Norway
Date(s) of inspection:	Onsite inspection from 09 – 11 October 2019. Document review continued office-based and was concluded on 14 October 2019.
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:	As part of the general systems review, specific ADR reports and PSURs were examined for [redacted] Both products are CAPs.
Name and location of EU QPPV:	[redacted] Contact details as above.
Global PV database (in use at the time of the inspection):	Oracle Argus safety (version 7.0.3 as of 13 November 2016 (commercially available).
Key service provider(s):	Pharmacovigilance services provided by United BioSource LLC (UBC). Medical information services provided by ProPharma Group.
Inspection finding summary:	6 Major finding(s) 5 Minor finding(s)
Date of first issue of report to MAH:	18 November 2018
Deadline for submission of responses by MAH:	06 January 2020 12 February 2020 21 February 2020 05 March 2020
Date(s) of receipt of	23 December 2019

Section 40

responses from MAH:	12 February 2020 21 February 2020 05 March 2020
Date of final version of report:	06 March 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

EUSA Pharma was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to 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.

EUSA Pharma is a global biopharmaceutical company headquartered in Hemel Hempstead, Hertfordshire with subsidiaries and branch offices across Europe and the US. Selected PV activities have been delegated by EUSA Pharma to their chosen contract safety organisation, UBC. EUSA Pharma retains responsibility for the oversight of the PV system and conducts PV activities alongside UBC such as Regulatory Affairs, Quality Assurance, Medical Affairs and Marketing/Commercial Affairs. UBC's responsibilities include case processing, aggregate safety report writing, employment of an EU QPPV, support for RMP development and preparation and maintenance of the PSMF.

Section 43

At the time of the inspection, EUSA Pharma held two EU marketing authorisations licensed via the centralised procedure:

- [redacted] – first authorised 08 May 2017, orphan medicine approved under exceptional circumstances. [redacted] is a mouse-human chimeric monoclonal [redacted] produced in a mammalian cell line (CHO) by recombinant DNA technology and is used to treat neuroblastoma.
- [redacted] – first authorised 24 August 2017. [redacted] is used in first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.

A transfer of the EU marketing authorisation for [redacted] from [redacted] and the handover of PV responsibilities for this product had just completed on 25 September 2019. This was also considered within the inspection scope.

At the time of the inspection the PSMF was located in Oslo, Norway, and the supervisory authority was the Norwegian Medicines Agency (Legemiddelverket).

B.2 Scope of the inspection

The inspection included a review of the local UK and global pharmacovigilance systems and was performed at EUSA Pharma's offices in Hemel Hempstead, Hertfordshire. Personnel from EUSA Pharma and UBC attended the Hemel Hempstead site in order to participate in the inspection. Additional personnel from UBC participated via teleconference to support the inspection.

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).

The role of the EU QPPV, RMPs and validation of computerised systems were not reviewed in detail but partly covered under other technical areas. Performance and activities surrounding medical information services was not reviewed in depth during the inspection and it is recommended that this area is subject to closer review during a subsequent pharmacovigilance inspection.

Section 43

B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] effective date 07 June 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 in document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. The inspection included an additional office-based inspection day, which was held on 14 October 2019 to review the documents provided after the on-site inspection.

A closing meeting was held to review the inspection findings at EUSA Pharma, Hemel Hempstead, on 11 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

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

C.2 Definitions of inspection finding gradings

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

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

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

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

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

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

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

No critical findings were identified from the review of pharmacovigilance processes, procedures and documents performed during this inspection.

C.4.2 Major findings

MA.1 Biological medicines

Requirements:

GVP Product- or Population-Specific Considerations II: Biological medicinal products

P.II.B.1.1.4 *'As a general principle in order to improve traceability of biological medicines, all summaries of product characteristics (SmPCs) for biologicals (also with relevant appropriate wording in the package leaflets (PLs)) should include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file.'*

P.II.B.4. *'Signal detection for biologicals should therefore be specific to the product, as well as the active substance. All steps of signal management should be performed at the level of the product name, as well as the active substance. In case of a signal any effort should be made to identify any common root cause such as batch.'*

'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.'

P.II.B.2. *'Competent authorities and marketing authorisation holders should also encourage reporters to record information on product names and batch numbers. A follow-up procedure should be put in place to obtain the batch number where it is not indicated in the initial report.'*

Section 43

"Unlike chemically synthesised medicines which can usually be easily characterised and reproduced across different manufacturers, biological active substances are complex molecules produced usually using complex manufacturing processes with many upstream or downstream steps that shape the overall safety, quality and efficacy profile. Minor changes in any manufacturing step can affect the product quality, and subsequently its safety and efficacy" [redacted]

Due to the inherent nature of biological products and the potential for manufacturing changes to impact upon the safety and efficacy of biological medicines, specific pharmacovigilance requirements and guidance has been laid out GVP chapter PII. This includes the requirement for batch-specific monitoring, actions to improve visibility that the product is a biological medicine (inclusion of statements in SPCs / PILs and any additional risk minimisation materials), and the necessity for batch information to be reported alongside adverse drug reactions.

EUSA Pharma is the MAH for [redacted] a biological medicine. As such the MAH is required to fulfil the obligations laid out in [redacted] and ensure these requirements are met for their recently acquired biological product, [redacted]

Section 43

Finding MA.1 a)
The current version of the EU SmPC (dated 11 March 2019) and PIL for [redacted] did not include prominent statements that the name and batch number of the administered product should be clearly recorded in the patient file. This is important to help improve traceability of biological medicines.
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 b)
There was no mechanism in place to allow the detection of any 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. Although EUSA Pharma stated in response to a document request concerning processes to inform pharmacovigilance staff of significant manufacturing changes that if a "planned change is significant with regards to safety, the global PV manager assessment will be requested as a subject matter expert", this was not formalised in a written procedure. There

was no mechanism for how changes that were "significant with regards to safety" would be identified.

Section 43

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 c)

Signals for [redacted] were not evaluated in the context of batch-specific exposure data, as per the requirements in GVP PII. There was no evidence in procedural documents or signal evaluation reports that any validated signals for [redacted] had been evaluated contextually with batch-specific exposure data.

In relation to finding MA.1 b), this is important as batch-specific reporting trends could pick up a potential risk arising from a change to the manufacturing process or quality of a biological product. No procedural documentation to support batch-specific analysis was available in the procedures for signal management.

Root Cause Analysis

[redacted]

Section 43

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

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

Preventative Action(s)
[redacted]

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

Finding MA.1 d)

There was no evidence of follow-up being performed to request batch numbers for reported ADRs where [redacted] had been used.

Two cases received for [redacted] were identified for which a request for follow-up information was sent but did not include a request for information on the batch number and expiry date:

- [redacted] a solicited case received from Israel on 08 May 2018 reporting that the patient had died without any further information. Requests for follow-up information were sent to the treating physician on 25 May, 05 June, 18 June and 19 June 2018 but these did not include requests for the batch number and expiry date. The case was eventually lost to follow-up.
- [redacted] two spontaneous cases received from the UK on 01 August 2019 reported drug hypersensitivity in two children. A request for follow-up information was sent to the reporter on 02 August 2019 but did not include a request for the batch number and expiry date. The cases were eventually lost to follow-up.

Furthermore, upon review of the adverse event line listing, which included all cumulative

Section 43

cases received, provided to the inspectors for the purpose of the inspection only [redacted] reported events had an associated batch ID from a total of [redacted] reported events for [redacted]

The requirement to follow-up for batch number and expiry date for EUSA's biological medicines was only included in version 7.0 of the Adverse Event Reporting Plan between UBC and EUSA which became effective on 26 August 2019.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Section 43

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

MA.2 Ongoing safety evaluation

Requirements:

GVP IX Signal management (Rev 1)

IX.B.5. *'A system of quality management (see GVP Module I) should be applied to all signal management processes. 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.'

Commission Implementation Regulation 520/2012, (10)
'Marketing authorisation holders, national competent authorities and the Agency should continuously monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the risk-benefit balance of the medicinal product. They should validate and confirm signals, as appropriate, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, literature information or other data sources.'

EUSA Pharma had contracted signal detection activities to UBC. UBC provided continuous monitoring of the safety profile for products and assisted in signal detection, evaluation and risk-benefit assessment. UBC were also responsible for conducting a review of EudraVigilance three times per-week for any relevant ICSRs.

In conjunction with EUSA Pharma, UBC reviewed consolidated safety data to assess overall safety profiles for products by way of the EUSA Pharma/UBC Safety Surveillance Committee. The Committee met bi-annually to review safety data and confirm any potential signals that had been evaluated by the Safety Monitoring Committee at EUSA Pharma.

Section 43

A separate [redacted] Safety Monitoring Committee had been established between EUSA Pharma and AVEO due to the co-licensing agreement between these parties.

The following findings were made in relation to signal management activities.

Finding MA.2 a)

There were examples of events identified in ICSRs retrieved from EudraVigilance that met the criteria to be validated as potential signals but had not undergone signal validation or been added to the signal tracker as the full narrative for the cases had not been requested.

As stated in the UBC Signal Detection/Management Plan [redacted] effective from 15 April 2019, and [redacted] effective from 2019 September 24), section 7.1.1. 'Signal detection: what to look for?': *"Examples of situations or findings that could qualify as a signal include [...] New unlabelled adverse events, especially if serious – striking case/index case" and "the events that should be closely monitored are the following: [...] Any unexpected events considering the known safety profile of the product*'.

Although there were events in these cases that met the validation criteria described in the

Section 43

SOP, further steps were not taken to obtain the cases in order to validate the signals. Examples identified are included below:

- Case [redacted] described a patient who experienced the following serious unlisted events after receiving [redacted] hemiparesis, gait disturbance, aphasia, agitation and facial paralysis. The case evaluation in the [redacted] signal detection slides (for the period 01 December 2019 – 28 February 2019) for the signal detection meeting on 28 March 2019 stated: "Despite the positive dechallenge and the suggestive time to onset, the missing narrative does not allow to perform a proper assessment".

- Case [redacted] described a patient who experienced the following unlisted serious events after receiving [redacted] coordination abnormal, balance disorder, confusional state and colour blindness. The case evaluation in the [redacted] signal detection slides (for the period 01 December 2019 – 28 February 2019) for the signal detection meeting on 28 March 2019 stated: "although there is suggestive temporal relationship (< 2 weeks) the case was poorly described, precluding a proper assessment (the original narrative from The Sender is not available)".

The company stated that in accordance with the EMA's access policy that the full ICSR including the narrative would only be downloaded when a signal is identified and needs to be validated. This conflicts with the approach in the examples above where the narrative was required to confirm a signal and progress to validation. Consequently, there is the potential that these identified safety concerns may require actions to be taken when they have been fully evaluated.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Section 43

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

Finding MA.2 b)

The criteria used to identify potential signals for review during the monitoring of EudraVigilance was not formally documented.

[redacted] EMA Eudravigilance Monitoring Using EVDAS/eRMR Tools [redacted] effective from 14 August 2018) included a flow chart titled 'eRMR medical analysis decision tree and classification' in attachment B. This flow chart represented the process of identifying signals through the review of the eRMR. Step one of the process required a Yes/No answer in response to whether the signal met the DEC analysis entry point. Section 4.0 of this work practice defined what the DEC entry point would be:

> *"the safety physician (assisted by the project specific team/governance as appropriate) will define which type of DEC will trigger a review (entry point for analysis)."*

The MAH stated to inspectors that the relevant criteria defined by safety physicians for determining the DEC type was as follows:

> *"New EVPM > 0 AND*
> *Total EVPM ≥ 3*
> *...*
> *The entry point is agreed upon and circulated via email with the UBC physicians assigned to the product and personnel involved in EUSA signal detection activities."*

Evidence was seen of consistent application of these criteria, however it was not formally defined in any procedures, including [redacted] EUSA Pharma Signal Detection/Management Plan [redacted] effective from 15 April 2019, and [redacted] effective from 2019 September 24).

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

MA.3 Pharmacovigilance Data Management

Requirements:

Commission Implementation Regulation 520/2012, Article 12

GVP I – Pharmacovigilance Systems and their Quality Systems

I.C.1.4. *"Documents transferred in situations where the business of the marketing authorisation holder is taken over by another organisation should be complete."*

GVP VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

VI.B.4. *"When transfer of pharmacovigilance data occurs within an organisation or between organisations having set up contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken."*

VI.B.5. *"…marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR submission and case archiving (see VI.C.6.2.4. and GVP Module I for EU guidance on data quality of ICSRs)."*

Section 43

EUSA Pharma completed the acquisition of the worldwide rights to [redacted] from [redacted] Sciences Ireland UC in December 2018.

The EU Marketing Authorisation approval for EUSA Pharma was 3 September 2019 and according to the Transition Project Timeline, EU PV Transfer occurred on 25 September 2019.

The finding observed during the inspection relates to the data management and record keeping regarding this transition.

Finding MA.3 a)

EUSA could not demonstrate compliance with the requirements for record keeping in accordance with Article 12 of the Commission Implementing Regulation EU 520/2012 for one of their EU authorised products.

In support of the transfer of pharmacovigilance activities for [redacted] from [redacted] to EUSA in September 2019, a data migration was conducted and completed in July 2019 as described in the Data Migration Summary Report (dated 10 September 2019). However, there was no ongoing contract in place with [redacted] hat permitted EUSA Pharma access to the source documents or stipulated [redacted] etention period for these documents. As a result, EUSA Pharma did not have access to any of the source documentation from the [redacted] cases transferred from [redacted] Further details of these cases are provided below:

- [redacted] are literature cases
- [redacted] are spontaneous cases
- [redacted] are clinical cases

Without access to this data, EUSA could not verify that record keeping requirements were

Section 43

being met in accordance with GVP I: I.B.10: Record management, or verify the accuracy of the data transferred from [redacted] against the source records in accordance with GVP IX: VI.B.4. Data management.

During the inspection, when asked if EUSA had access to the original source documents for these cases a written response from [redacted] was provided which cited the requirements in the General Data Protection Regulation (EU) 2016/679 (GDPR). It should be noted that, in accordance with Article 6 of GDPR, processing of the data is lawful in circumstances including where "*necessary for compliance with a legal obligation to which the controller is subject*" and where "*necessary for the performance of a task carried out in the public interest*".

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]	

MA.4 Management and Reporting of Adverse Reactions

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

VI.B.2. *'Similarly, the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance a marketing authorisation holder is made aware that a patient was hospitalised or died, without any further information. In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event.'*

VI.B.5. *'Competent authorities and marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as [...] data management, data coding [...].'*

Section 43

During the inspection, 20 ICSRs were reviewed which included [redacted] as a suspect drug. At the time of inspection, there were just over [redacted] cases for [redacted] n the safety database.

The following findings were noted in relation to management and reporting of adverse reactions:

Finding MA.4 a)

A case was incorrectly submitted to EudraVigilance. [redacted] was a solicited case received from Israel on 08 May 2018 that reported the patient had died without any further information. The case was reported to EudraVigilance on 16 May 2018 despite not meeting the minimum reporting criteria. GVP VI states that for outcome only cases, these should not be submitted to EudraVigilance as they are not a valid ICSR.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Preventative Action(s)

[redacted]

Section 43

[redacted]

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

Finding MA.4 b)

In relation to the expectedness assessment for [redacted] discrepancies were seen between the correct assessment of events against the ADRs listed in the EU SmPC section 4.8 *Undesirable effects* (dated 11 March 2019 and the previous version dated 06 March 2018). The following examples were identified:

- PT 'confusional state' was incorrectly assessed as listed for case [redacted] (received 18 March 2018) even though this PT was not included in the SmPC.
- PT 'Acute respiratory distress syndrome' was incorrectly assessed as listed for case [redacted] (received 20 June 2019) even though the PT was not included in the SmPC.
- PT 'Hepatotoxicity' was incorrectly assessed as listed for cases [redacted] (received 18 May 2018) and [redacted] even though the PT was not included in the SmPC.
- PT 'respiratory failure' was incorrectly assessed as unlisted for case [redacted] (received 10 December 2018) even though the PT was included in the SmPC.

EUSA Pharma's Signal Detection/Management Plan [redacted] effective from 30 September 2019 (unchanged from [redacted] effective from 15 April 2019)), stated in section 7.1.1 that any "*New unlabelled adverse events*" arising would be used to identify potential signals. Therefore, the impact on the inclusion or omission of any events with incorrect expectedness assignment in signal detection activities should be considered in the further assessment.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

[redacted]	

Finding MA.4 c)

The UBC-EUSA Adverse Event Reporting Plan [redacted] (effective from 31 August 2018), section 6.16. *Awaiting Follow-up and Due Diligence the timeframes involved for follow-up activities*, states that for both serious and non-serious cases, the first attempt for follow-up should be done within 15 calendar days from receipt date.

Minor delays were seen in sending out requests for follow-up information for the below cases, which deviate from the timeframes laid out in company procedures:

- [redacted] was a non-serious, spontaneous case from Ireland received on 20 June 2019 reporting eye disorder and product intolerance. The first attempt for requesting follow-up information was sent on 16 July 2019 representing a delay of 8 days.
- [redacted] was a serious, spontaneous case from Israel received on 18 February 2019 reporting death. The first attempt for requesting follow-up information was sent on 12 March 2019 representing a delay of 7 days.
- [redacted] was a serious, spontaneous case from France received on 22 May 2019 reporting acute kidney injury, adenovirus infection and varicella. The first attempt for requesting follow-up information was sent on 11 June 2019 representing a delay of 5 days.
- [redacted] was a serious, spontaneous case from Israel received on 08 May 2018 reporting death. The first attempt for requesting follow-up information was sent on 25 May 2018 representing a delay of 2 days.
- [redacted] was a non-serious, spontaneous case from Croatia received on 24 August 2018 reporting hypothyroidism. The first attempt for requesting follow-up information was sent on 11 September 2018 representing a delay of 1 day.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment
[redacted]

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

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

MA.5 Post-authorisation Safety Study

Requirements:

GVP Module VIII – Post-authorisation safety studies (Rev 3)

VIII.B.2. *"the marketing authorisation holders should also enter in the EU PAS Register all non-interventional PASS required in the risk management plan agreed in the EU or conducted voluntarily in the EU."*

"The study protocol should be uploaded as soon as possible after its finalisation and prior to the start of data collection. Updated study protocols in case of substantial amendments, progress reports and the final study report should also be entered in the register (as soon as possible and preferably within two weeks after their finalisation)."

Section 43

Finding MA.5 a)

EUSA Pharma had not uploaded the protocol for the category 2 PASS: "A Post-Authorisation Safety Study Patient Registry of patients with high-risk neuroblastoma being treated with the [redacted] into the EU PAS register. The [redacted] RMP ([redacted] approved 29 March 2017) detailed the category 2 study which was aimed to further evaluate the efficacy and safety of dinutuximab beta in patients with neuroblastoma.
The protocol [redacted] had been approved on 23 April 2018 by the PRAC but was not yet uploaded to the EU PAS Register.

At the time of inspection sites for the study had been identified across the EU, including the UK, and were in the process of being initiated. No data had yet been collected for this study.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

Preventative Action(s)
[redacted]

[redacted]	

MA.6 Pharmacovigilance System Master File

Requirements:

Commission Implementing Regulation 520/2012

Article 3 *"Content of the Annex to the pharmacovigilance system master file*
The pharmacovigilance system master file shall have an Annex containing the following documents: …
(5) a list of all scheduled and completed audits;
(6) where applicable, a list of the performance indicators referred to in Article 9"

GVP II – Pharmacovigilance system master file (Rev 2)

II.B.4.6. *"Targets for the performance of the pharmacovigilance system shall be described and explained. A list of performance indicators must be provided in the Annex to the PSMF [IR Art 3(6) and Art 9], alongside the results of (actual) performance measurements."*

II.B.4.7. *"A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to II.B.4.8. [IR Art 3(5)]. This list should describe the date(s) (of conduct and of report), scope and completion status of audits …"*

Section 43

Finding MA.6

Several deficiencies were observed in the Annexes of the PSMF [redacted] (effective date 07 June 2019) provided for the purposes of inspection planning. Although these were not observed to impact on the performance of pharmacovigilance activities, the deficiencies are a breach of the legislative requirements and impacted on the planning of the inspection.

i. The KPIs included in Annex F1 (version [redacted] 13 November 2015 and [redacted] 31 December 2018) of the PSMF did not specify thresholds for the KPIs to be monitored against. It is acknowledged that the performance measurement of >98% for ICSRs was included in the main PSMF body, section 6: *Pharmacovigilance System Performance*.

ii. Annex G2 List of Audits Completed and Conducted of the PSMF [redacted] (effective date 16 September 2019) did not provide the audit report date, audit scope and completion status of audit.

Root Cause Analysis

[redacted]

Section 43

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

C.4.3 Minor findings

MI.1 Periodic Safety Update Reports

The following minor findings were noted in relation to PSURs:

Section 43

Finding MI.1 a)

Errors were found in the [redacted] PSUR No. 3, Appendix 3 *Cumulative And Interval Summary Tabulations Of Serious And Non-Serious Adverse Reactions From Post-Marketing Data Sources* (PSUR interval 24 August 2018 - 23 February 2019, dated 18 April 2019).

i. Non-serious adverse reactions of mucosal inflammation and hypertension from solicited case [redacted] were incorrectly included in the column that listed the spontaneous cases received in the PSUR interval even though the case was received from the Italian Expanded Access Programme on 12 October 2018.
The Expanded Access Programme (conducted in Italy to supply [redacted] in this territory) started in August 2018. However, neither EUSA Pharma's global pharmacovigilance department nor UBC had been informed of the programme until 8 months after the start date. Therefore, the case was erroneously included as a spontaneous case in the safety database.
It should be noted that the case type for [redacted] was amended from spontaneous to solicited in the meantime since the DLP of the PSUR, 23 February 2019.

Post-inspection request: In the next [redacted] PSUR summary tabulation, any changes in the inclusion of adverse event terms in comparison to the previously submitted PSUR should be highlighted and explained to the assessor.

ii. The adverse reactions 'diarrhoea haemorrhagic' and 'gastrointestinal haemorrhage' received from solicited cases [redacted] of the AVEO compassionate use programme [redacted] in the PSUR interval were incorrectly included in the 'SOC General disorders and administration site conditions' whereas they should have been listed under the primary 'SOC Gastrointestinal disorders'. Each PT included one count of the respective event.
It should be noted that both PTs were also listed under the correct SOC, but no adverse event report counts were associated with them.

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]	

Finding MI.1 b)
[redacted] PSUR No. 4 (PSUR interval 09 November 2018 – 08 May 2019, dated 05 July 2019) Appendix 1 *Reference Information* did not include a copy of the SmPC but only the statement '[redacted] SmPC dated 11 March 2019". In line with GVP VII.B.4. Reference Information, the full SmPC should be included in the PSUR: *"The marketing authorisation holder should provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR) as an appendix to the PSUR (see VII.B.5.20.). The reference product information should be dated and version controlled."*
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Section 43

[redacted]

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

MI.2 Reference Safety Information

Section 43

Finding MI.2 a)
A signal was identified at the 8-11 July 2019 PRAC meeting for vascular endothelial growth factor (VEGF) inhibitors (including [redacted] and arterial dissection/aneurysms. Subsequently the PRAC provided recommended wording to be used in updated product information was published on 06 August 2019. It was stated that MAHs should "should submit a variation within two months" to amend the product information, which infers a deadline of 06 October 2019. Although, the update had been approved internally at EUSA on 06 October 2019, a Type IAIN variation (immediate notification) was not submitted by EUSA until 7 October 2019, one day outside of this timeframe.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Finding MI.2 b)

Timeframes to ensure the timely implementation of updates to leaflets into production were not formalised in a written procedure. Although it was stated in response to a document request that it would be defined in the kick-off meetings and change controls, the requirement for having documented procedures and processes for this activity is laid out in Commission Implementing Regulation (EU) No 520/2012, Article 11 (1):
"*Specific quality system procedures and processes shall be in place in order to ensure the following: […](f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal;*"

Section 43

In order to implement the PRAC recommended wording to the SmPC and PIL for [redacted] Change control request (CCR) [redacted] (approved 29 August 2019) described the actions and due dates for implementing these changes. The CCR stipulated that no packs with "old" leaflets should be released after 06 October 2019, and the implementation of new leaflets in all packaging campaigns of products to be released from 07 October 2019. However, the commencement of circulation for the updated SmPC and leaflet was not due until 11 January 2020 "upon receipt of approval", which is contradictory to the company's planned implementation of new leaflets from 07 October 2019.

It should be noted that [redacted] variations do not require approval from EMA prior to their implementation.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

Section 43

[redacted]

MI.3 Auditing of the Pharmacovigilance System

Audit management at EUSA Pharma was split between internal pharmacovigilance processes and external partners to which PV activities had been subcontracted. As a result, separate procedures were followed to establish the audit universe, risk assessment and audit scheduling for internal pharmacovigilance processes and external pharmacovigilance partners.

Minor deficiencies were observed in relation to audit planning for both internal processes and external partners.

Section 43

Finding MI.3 a)
There was insufficient procedural guidance on how the risk scores assigned to auditable PV systems at EUSA during the internal audit risk assessment process mapped to the scheduling of audits in the annual audit plan. [redacted] *Internal Audit* (effective from 13 April 2019) did not provide guidance on how the audit frequency could be determined based on the risk score. [redacted] section *4.2 Risk-Based Assessment for Audit Frequency* included a guideline on the pre-defined audit frequencies of semi-annually, annually or biennially for different pharmacovigilance processes. In addition, it stated: "*The areas to be audited should be ranked according to the level of the risk according to the method as described in* [redacted] *for risk events [...] Audit frequency may be changed based on the outcome of the risk analysis except for audits on safety processes, BCP/DRP testing and testing of the mock recall procedure.*" No further information was provided in the procedures on how the pre-defined audit frequency would be amended based on risk assessment scores which is outside of the guidance in GVP IV: *"The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme should be based on the documented risk assessment."*
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
[redacted]

Section 43

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

Finding MI.3 b)

There was insufficient procedural guidance on how the PV partner risk assessment process for should be carried out in support of the audit scheduling.

i. Since May 2019 PV partners considered for audit were supplied with a PV Risk Assessment Questionnaire and EUSA reviewed their responses to grade responses as low, medium or high risk which would eventually feed into the overall risk score for audit planning. However, [redacted] Partner Pharmacovigilance Risk Assessment (effective from 20 September 2019) describing this process was only approved on 30 September 2019 whereas the PV Risk Assessment Grid documenting the questionnaire results was completed on 24 May 2019, four months before the working instruction was finalised. As a result, there is no assurance that staff consistently graded responses appropriately, impacting on the final risk score of a PV partner and therefore audit planning. Prior to May 2019, PV partners were risk assessed and considered for audit as described in [redacted] Contractor and External Audit Programme (effective from 01 May 2018) but this procedure did not include any guidance on assessment of questionnaire responses.

[redacted] Partner Pharmacovigilance Risk Assessment (effective from 20 September 2019) did not include sufficient guidance on the process to follow if partners did not respond to the PV Risk Assessment Questionnaire after three follow-up requests from EUSA Pharma. The MAH stated that in practice, these companies would be considered high-risk and acknowledged this should have been included in [redacted].

One example was identified where a partner had not responded to the PV Risk Assessment Questionnaire. The external study research sponsor for [redacted] CCRI, was included in the 2019 risk assessment process and despite three follow-up requests, did not return the completed questionnaire.
In the PV Risk Assessment Grid 2019, CCRI were not given a final risk score and were not included in the Risk Assessment for External Audits [redacted] EUSA Pharma confirmed in response to a document request that CCRI was subsequently graded as high-risk but were not included in the audit schedule due to ongoing contractual discussions. However, this information had not been captured in either document.

As no other examples were present where a PV partner had not responded past the three follow-up attempts and as EUSA Pharma demonstrated adequate handling of the CCRI scenario, this is classified as a minor finding as there was no impact on audit scheduling.

Root Cause Analysis

[redacted]

Section 43

[redacted]

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

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

Finding MI.3 c)
One example was identified of an audit report not being sent to the QPPV. The audit report for external audi[redacted] (the qualification audit of the medical information services ([redacted] conducted 28 March 2018) was not shared with the QPPV and this is outside of GVP IV.C.1. which states: *"The QPPV should be notified of any audit findings relevant to the pharmacovigilance system in the EU, irrespective of where the audit was conducted."* As this was the only audit report incorrectly not shared with the QPPV and no critical or major findings were reported from this audit, this is classified as a minor finding.
Root Cause Analysis

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

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

MI.4 Oversight of the Pharmacovigilance System

Section 43

Finding MI.4 a)
UBC provided a monthly metrics report to EUSA Pharma which gave an oversight of the activities undertaken on behalf of EUSA Pharma. As part of the metrics, KPIs were measured in relation to the number and percentage of AE reports sent from [redacted] to [redacted] within 24 hours and the number and percentage of Medical Information Quality Assurance Reconciliation sent on time to UBC. For both KPIs, no threshold had been defined which would trigger further action. For example, the overall compliance was [redacted] in 2018 for the Medical Information reconciliation taking place on time. Whenever KPIs are in place, a target threshold value should be defined so that resolutive actions can be triggered.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MI.4 b)
In order to monitor performance of the PV system and set objectives for the Quality team, EUSA developed reports for periodic Quality Management Reviews (QMR) and Annual Product Quality Reviews (APQR). The QMR included metrics and information on complaints, deviations, CAPAs, audits and manufacturer surveillance across all functional areas at EUSA, including PV activities. The APQRs were developed for each product, [redacted] and provided a periodic and retrospective overview of the processes and data obtained from manufacturing to release of the products, taking information from

relevant contractor's own performance reports. In terms of pharmacovigilance activities, the APQR served to provide a review and assessment of any relationship between product complaints and reported adverse events.

There was evidence of deviations from internal procedures relating to the development and review of the QMR reports and APQRs:

Section 43

i. [redacted] CAPA management (effective from 07 June 2019), [redacted] Internal Audit (effective from 13 April 2019) and [redacted] Management of Deviations (effective from 07 June 2019), stated under the section "Quality Indicators" that the QA Department would prepare quality metrics on a periodic basis (usually quarterly) for the EUSA Leadership Team. The company provided evidence that a QMR had been completed on 06 September 2019 for the period 01 January 2018 to 31 June 2019 but confirmed that quarterly quality metrics were not being provided since approval of the MAs for Qarziba and [redacted]

ii. There were significant delays of over 11 months in the authoring and review of the [redacted] APQRs:

- Review and approval of the [redacted] 2017/2018 APQR was delayed by over 11 months following the authored date. The APQR was authored on 19 October 2018 but was not reviewed and approved until 08 October 2019.
- The [redacted] 2017/2018 APQR was authored just over 7 months after the receipt date of the relevant contractor's report. The contractor's report was received on 31 January 2019 but the APQR was not authored until 08 October 2019.
- The [redacted] 2016/2017 APQR was not authored until 06 May 2019. There was also a discrepancy between the review date (08 October 2019) and approval date (07 August 2019) of the APQR as it was approved before being reviewed.

EUSA's internal procedure [redacted] *Annual Product Quality Review* (effective from 01 April 2017) and its predecessor [redacted] (effective from 01 September 2016) stated:

"The Annual Product Quality Reviews for each product(s) are compiled and reviewed annually. The APQR should cover a one-year review period but does not have to coincide with the calendar year."

"Within 30 business days of receipt of the APQR report(s) from the Contractor, the QA Manager shall review the Contractor's report and data obtained and initiate EUSAPharma's internal Annual Product Quality Review Report for the product(s)."

Although the two above deviations could imply insufficient oversight of performance, it was confirmed during the inspection that sufficient oversight of these activities occurred routinely through the PV/QA bi-monthly meetings, where CAPAs, qualification of new partners, training, deviations and audits were discussed.

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]	

MI.5 Quality Management System

Section 43

Finding MI.5 a)
The procedure in place to manage deviation related CAPAs did not include sufficient guidance on timely closure of the CAPAs in the quality management system. [redacted] *Management of Deviations* (effective from 07 June 2019) did not define the timelines for closing CAPA records in their quality management system following completion of the CAPA. The following examples were seen where the CAPA were completed but had not been closed in EUSA's deviation and CAPA management system. As a result, these CAPA were still recorded as open in the PSMF [redacted] (effective date 16 September 2019) Annex G2 even though the actions had been completed: • [redacted] – completed 07 June 2018 • [redacted] – completed 19 September 2018 (monthly PVQA meeting held from this point onwards)
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

C.4.4 Comments

Section 43

1. In relation to [redacted] PSUR No. 3, section 5.2. *Cumulative and Interval Patient Exposure from Marketing Experience* it was noted that the data included in this section is taken from an interval period not matching the PSUR interval: the sales data used covered the period from 01 September 2018 to 28 February 2019, whereas PSUR interval covered the period from 24 August 2018 to 23 February 2019.
Although the impact of this discrepancy is very low, this should be highlighted to the PSUR assessor in the relevant section of the next PSUR.

2. The SDEA tracker referenced in Annex B2 of PSMF [redacted] (effective date 07 June 2019) which included a list of all contractors/partners with whom an SDEA was in place, was not provided to MHRA inspectors as requested prior to the start of the inspection to aid inspection planning. In line with GVP Module III, it is the MAH's responsibility *"to make available to the inspectors any information and/or documentation required for the preparation of the inspection".* Of note, the SDEA tracker was included in the later version of the PSMF (v.13, effective date 16 September 2019) provided to the inspectors on day 1 of the inspection.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- 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 44185/11625545-0004	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	EUSA	**DATE**	09 October 2019
LOCATION	3rd Floor, Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ	**START TIME**	09:00 arrival for 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 include any ongoing remediation processes for the pharmacovigilance system. *(approx. 20 minutes)*	[redacted]	[redacted]
Document collation and review	-	Inspectors only
LUNCH	-	-

Section 40

Section 40

Sources of safety information *Including but not limited to:* • Medical enquiries • Product quality complaints • Literature • EudraVigilance • SDEAs • Managed access programmes, named patient supply and investigator initiated studies	[redacted]	[redacted]

Section 40

ICSR management *Including but not limited to:* • Data entry • MedDRA coding • Case assessments • Follow-up processes • Expedited reporting	[redacted]	[redacted]
N.B. The inspection plan may need to be amended during the inspection. [redacted]		

MHRA INSPECTION NUMBER	Insp GPvP 44185/11625545-0004	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	EUSA	**DATE**	10 October 2019
LOCATION	3rd Floor, Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Identification and management of non-compliance *Including but not limited to:* • Audits • Deviation and CAPA management	[redacted]	[redacted]
Ongoing safety evaluation *Including but not limited to:* • Signal detection, validation, evaluation and tracking	[redacted]	[redacted]
LUNCH	-	-

Section 40

Section 40			
	PSURs	[redacted]	[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 44185/11625545-0004	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	EUSA	**DATE**	11 October 2019
LOCATION	3rd Floor, Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Post-authorisation safety study	[redacted]	[redacted]
Document review and ad hoc questions	-	Inspectors only
LUNCH	-	-
Closing meeting	-	[redacted]

Section 40