Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Eisai Limited

MHRA Inspection Number: Insp GPvP 10555/830938-0015

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
ECL	Eisai Corporation Limited (Headquarters, Japan)
EEL	Eisai Europe Limited (EMEA regional and UK local offices)
ESI	Eisai, Inc. (Americas regional and USA local offices)
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium
eRMR	Electronic Reaction Monitoring Report
EU	European Union
GSO	General Safety Officer
GVP	Good Vigilance Practice
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
LL	Line Listing
LSO	Local Safety Office
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PSMF	Pharmacovigilance System Master File
PSP	Patient Support Programme
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
RSO	Regional Safety Office
SAE	Serious Adverse Event

SDEA	Safety Data Exchange Agreement
SDR	Signal of Disproportionate Reporting
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Eisai, [redacted]
Site(s) of inspection:	Eisai Europe Limited European Knowledge Centre Mosquito Way Hatfield AL10 9SN
Main site contact:	[redacted]
Date(s) of inspection:	17 – 20 February 2020 (onsite inspection)
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	CHMP-requested inspections: 29 April – 02 May and 19 – 21 May 2014 11 – 13 August and 28 September – 01 October 2009 MHRA routine inspections: 29 April – 03 May 2013 22 – 25 July 2008 19 – 23 March 2007 09 – 11 January and 01 – 02 February 2006
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements
Name and location of EU QPPV:	[redacted]
Global pharmacovigilance database (in use at the time of the inspection):	Global Product Safety Surveillance System (Global PSSS), based on an Adverse Reaction Information System Global (LSSMV, formerly ARISg) and LifeSphere Safety Electronic Submissions (LSES, formerly agXchange ESM) (commercially available database).
Key service provider(s):	Medical information services provided by ESMS Global Limited. Advanced Medical Services (AMS) provided CRO services for local non-interventional study [redacted] All other key pharmacovigilance activities are performed in-house by the MAH.
Inspection finding summary:	02 Major findings 07 Minor findings

Date of first issue of report to MAH:	24 March 2020
Deadline for submission of responses by MAH:	30 April 2020. Extended by the lead inspector to 14 May 2020. Clarifications due 10 July 2020. Further clarifications due 06 August 2020. Further clarifications due 14 August 2020.
Date(s) of receipt of responses from MAH:	Initial responses received 13 May 2020. Updated responses received 10 July 2020. Updated responses received 06 August 2020. Updated responses received 11 August 2020.
Date of final version of report:	17 August 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Eisai Limited 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 (EC) No 726/2004 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.

Eisai is a global innovator pharmaceutical company headquartered in Tokyo, Japan with regional safety offices (RSOs) located in the USA, Asia and Europe. At the time of inspection planning, the location of the PSMF was Hatfield, UK. However, on 27 January 2020, three weeks prior to the start of the inspection, the location of the PSMF was changed to Frankfurt, Germany, the site of the EU QPPV.

Eisai have 88 products licensed in the UK, comprising 10 active medicinal substances. Of these, 80 are authorised via a centralised procedure and eight are authorised via a mutual recognition procedure. Eisai's product portfolio focuses primarily on the areas of oncology and neurology.

Pharmacovigilance activities for products authorised in the EU are conducted in-house, with the exception of medical information services that are outsourced to ESMS Global Ltd.

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at Eisai's offices in Hatfield, Hertfordshire. Personnel from the EMEA RSO (referred to as EEL) and the Japanese RSO (referred to as ECL) attended the Hatfield site in order to participate in the inspection, while personnel from the Americas RSO (referred to as ESI) were available via teleconference.

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

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version 36, 08 January 2020) to assist with inspection planning and preparation. Additional documents were requested by the inspection team and provided by the company prior to the inspection, details of which are contained within document request sheet A.

B.4 Conduct of the inspection

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

A closing meeting was held to review the inspection findings at the European Knowledge Centre, Hatfield on 20 February 2020. A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

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

Since the previous MHRA inspection in 2014, the company had made the following changes to the pharmacovigilance system:

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- Global Safety database upgrade: Transitioned to ARISg Multi–Tenant SaaS (LifeSphere), E2b R3 compliant system in March 2019
- Change in EU QPPV to [redacted] on 22 May 2019 (previously [redacted]
- Change in location of EU PSMF from Hatfield, UK to Frankfurt, Germany on 27 January 2020. The UK has however remained the main site for European pharmacovigilance activities.

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 Management and reporting of adverse events (AEs) and adverse drug reactions (ADRs)

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 27 "*Individual case safety reports shall be used for reporting to the Eudravigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time.*"

GVP Module VIII – Post-authorisation safety studies (Rev.3)
VIII.B.6 "*For non-interventional PASS imposed as an obligation, 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 [...] This provision should be also followed for PASS required in the risk management plan agreed in the EU or conducted voluntarily in the EU.*"

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)
VI.C.2.2.2. Solicited reports "*For all solicited reports, the marketing authorisation holder should have mechanisms in place to record and document complete and comprehensive case information and to evaluate that information, in order to allow the meaningful assessment of individual cases and the submission of valid ICSRs [...] The marketing authorisation holder should therefore exercise due diligence in establishing such system, [...] in seeking the view of the primary source as regards the causal role of the studied (or supplied) medicinal product on the notified adverse event. Where this opinion is missing, the marketing authorisation holder should exercise its own judgement to perform a causality assessment based on the information available in order to decide whether the report is a valid ICSR, which should be submitted in accordance with the time frames and modalities presented in VI.C.3., VI.C.4. and VI.C.6.*"

VI.B.2. Validation of reports "*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.*"

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Finding MA.1 a)

From a sample of six reports from the non-interventional PASS [redacted])', five examples were identified where events/reactions to a medicinal product that had occurred in a single patient at different points in time had been incorrectly amalgamated into one report, resulting in multiple submissions to authorities that were not all required.

[redacted]

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[redacted]

As an example, [redacted] which was initially received by Eisai on 19 June 2017, reported the following events:

- Serious event of leukopenia (onset date 06 June 2017)
- Serious event of hypokalaemia and non-serious event of diarrhoea (onset date 21 July 2017)
- Serious events of dyspnoea and malaise (onset date 26 August 2017)
- Non-serious event of polyneuropathy (onset date 10 September 2017)
- Serious events of cough and febrile infection (onset date 17 October 2017)
- Non-serious event of visual impairment (onset date 10 November 2017)
- Non-serious event of fatigue (onset date 08 January 2018)
- Serious event of disease progression with fatal outcome (onset date 22 Jan 2018)

In total, 21 versions of the case were created, seven of which were submitted to the EMA.

The [redacted] PASS concerns the company's product, [redacted] which is indicated for the treatment of locally advanced or metastatic breast cancer and is administered to patients intravenously on days 1 and 8 of every 21-day cycle.

The company should consider whether this has affected cases from other sources in the global safety database.

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]	
[redacted]	

Finding MA.1 b)

There were examples of MedDRA Preferred Terms (PTs) where the number of SAEs in the line listing (LL) provided in response to inspection request [redacted] PASS reports) did not match the number of SAEs presented in Table 10-29 'Serious adverse events by SOC, CTCAE, Preferred Term and mortality' in the interim study report for the [redacted] PASS (dated 15 November 2019). This was a Category 3 PASS required as per the EU RMP.

Examples of specific discrepancies were as follows:

- Malignant neoplasm progression:
  - 50 case IDs with this serious PT in the LL
  - 36 SAEs of any grade referenced in Table 10-29
- Pleural effusion
  - 10 case IDs with this serious PT in the LL
  - 7 SAEs of any grade referenced in Table 10-29
- Dyspnoea
  - 11 case IDs with this serious PT in the LL
  - 8 SAEs of any grade referenced in Table 10-29

The MAH was not able to provide an explanation for the discrepancies during the inspection, and therefore it is not known whether Table 10-29 of the interim report was inaccurate, whether the line listing provided to the inspectors was inaccurate, or whether there were valid explanations for the observed discrepancies.

It should be noted that reports from this study containing SAEs were selected based on the following criteria:

- The receipt date of the case version that first included a serious event was prior to the interim analysis data cut-off of 01 June 2019.
- Section 10.6.5 (Summary of serious adverse events (SAEs)) of the interim report did not state that only treatment emergent adverse events were included in Table 10-29, therefore all SAEs received prior to 01 June 2019 were counted by the inspector.
- Both related and not related events were counted.

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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]	

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Finding MA.1 c)
The reconciliation of safety data between the clinical and safety databases for the [redacted] PASS had not been documented as per the 'SAE and Adverse Events of Special Interest Reconciliation Plan' [redacted] 26 January 2017). • Section 3.1 'AMS Responsibilities' stated *"AMS is responsible for ensuring that all SAEs, (S)ADRs and AESI are reconciled for the clinical study prior to interim database lock and final database lock by generating SAE, (S)ADR and AESI Discrepancy Reports, reviewing it jointly with Eisai PV, and processing data queries as needed."* • Section 3.1 also stated *"AMS is also responsible for generating the SAE, (S)ADR and AESI Summary Report for sign off when the Reconciliation process is finished for interim analysis and final analysis separately."* An interim analysis report for this study was finalised on 15 November 2019. However, an 'SAE, (S)ADR and AESI Summary Report' for the interim reconciliation activity had not been generated. The only documentation available was the 'SAE, (S)ADR and AESI Discrepancy Report', which highlighted discrepancies for several hundred case IDs. There was no evidence to support that these discrepancies had been adequately resolved prior to preparation of the interim study report.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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[redacted]

Preventative Action(s)

[redacted]

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

Finding MA.1 d)

Three case examples were identified where no causality assessment had been conducted by the MAH for solicited reports containing non-serious events received from EU countries. In all three reports, the reporter had not provided a causality assessment for the non-serious events and the company assessment of causality had not been completed in order to determine reportability to EudraVigilance:

- [redacted]– German report of [redacted] and the non-serious events of hypertension, gingival bleeding and diarrhoea with off-label use. A serious event of seizure was also reported and assessed as not related by the MAH.
- [redacted] UK report of [redacted] and the non-serious event of headache with use of the product in an unapproved indication. A serious event of device related sepsis was also reported and assessed as not related by the MAH.
- [redacted]– German report of [redacted] and the non-serious event of aggravated malignant neoplasm with use of the product in an unapproved indication.

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 e)

Three adverse event reports were incorrectly reported to the MHRA despite not meeting the minimum reporting criteria. The cases reported the outcome of death only with no further information provided:

- [redacted] – spontaneous report from Brazil regarding [redacted] received 21 March 2017 and reported to the MHRA on 21 March 2017. A request for follow-up information was sent on 23 March 2017 to the company employee who had initially received the report from the healthcare professional, however this only requested further information on the start and end dates of [redacted] treatment, not on the circumstances of the patient death.

- [redacted] – solicited report from the USA regarding [redacted] received on 30

March 2017 and reported to the MHRA on 30 March 2017. A request for follow-up information was sent on 30 March 2017 but no response was received.

- [redacted] – spontaneous report from Mexico regarding [redacted], received on 02 June 2017 and reported to MHRA on 02 June 2017. The reporting physician was unable to be contacted for follow-up, and hence a follow-up request was not sent.

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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]

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[redacted]

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

MA.2 Pharmacovigilance system master file

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 4(3) *"Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved."*

GVP Module II – Pharmacovigilance system master file (Rev.2)
II.B.4.8. *"An annex to the PSMF shall contain the following documents:*

- *A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s), and the Member State(s) in which the authorisation is valid [IR Art 3];*

  The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation: […]

  - other (non EU) territories where the product is authorised or on the market […]

- *A list of contractual agreements covering delegated activities including the medicinal products and territory(ies) concerned […]*

- *A list of all completed audits, for a period of five years, and a list of audit schedules"*

  (emphasis added)

II.B.6. *"The PSMF shall be continuously accessible to the QPPV [IR Art 7(2)] and to the competent authorities on request [REG Art 16(3a), DIR Art 23(4), IR Art 7]. The information shall be succinct, accurate and reflect the current system in place […]"*

Finding MA.2 a)

The PSMF did not include any ongoing major or critical deviations from regional or local pharmacovigilance procedures. The criteria used by Eisai for inclusion of deviations in PSMF Annex G2 was "*Any ongoing major/critical deviations from Corporate SOPs*", as stated in the header of Annex G2. The following example of an ongoing major deviation from a local pharmacovigilance procedure that was not included in the PSMF was identified:

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[redacted] Major deviation from [redacted] 'Pharmacovigilance: généralités'. The French local safety office (LSO) pharmacovigilance team had only become aware of a local non-interventional study 'Use of [redacted] in routine psychiatric practice in schizophrenic patients' following receipt of the first adverse event report from this study, which was nine months after study initiation. The deviation was identified on 08 February 2019, the deviation report was finalised in August 2019 and the due date for CAPA completion is 30 June 2020. To note, this deviation was added to the PSMF in August 2019 but removed in October 2019 by the EMEA RSO, as it was not consistent with the current Eisai requirements for Annex G2.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

Finding MA.2 b)

Annex H1 'List of Products covered by the Pharmacovigilance System' ([redacted] October

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2019) included information on non-EU territories where the product was authorised or on the market; however, the following information was missing:

- [redacted]
  - Eisai was MAH for the product in Canada
  - Non-Eisai territories included Japan (MAH: [redacted] and South Korea [redacted]
- [redacted]
  - Non-Eisai territories included Argentina (MAH: [redacted]
- [redacted]
  - Non-Eisai territories included Bulgaria, Croatia, Greece and Namibia (MAH: J[redacted]

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.2 c)

PSMF Annex B4 'List of contracts' (version 39, October 2019) contained incomplete information on the territories in which pharmacovigilance responsibilities were delegated to partners. The following examples were identified:

- The SDEA between Eisai and [redacted] (dated 10 July 2019) specified the relevant territories for both partners concerning [redacted] in Exhibit B; however, Annex B4 only stated 'global' in the column titled 'Territory'.

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- The 'Agreement for the Exchange of Drug Safety Information' between [redacted] and Eisai (dated 05 October 2015) specified the relevant territories for both partners concerning [redacted] in Attachment 4; however, Annex B4 only stated 'global' in the column titled 'Territory'.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

Finding MA.2 d)

Documentation of audits in PSMF Annex G1 did not include scheduled audits and was not up to date on MHRA request.

i. As per the [redacted] pharmacovigilance audit plan (01 April 2019 - 31 March 2020), 13 audits had been scheduled. However, PSMF Annex G1 (version 54, November 2019) only included details of the nine audits scheduled up to November 2019. Scheduled audits of the following entities were not included: EM [redacted] (third party) and [redacted]

ii. Annex G1 was not an accurate reflection of the current audit status at the point of PSMF request by the MHRA. The PSMF was initially requested by the MHRA on 02 January 2020 and received on 09 January 2020; a further request for an up to date

version of the PSMF and annexes was requested on 29 January 2020 and received on 12 February 2020. The status of the following audits was inaccurate at the time of request:

- EEL routine pharmacovigilance audit: completion status 'audit pending', however audit was completed on 18 - 21 November 2019.
- EFS routine pharmacovigilance audit (conducted 15 - 16 October 2019): completion status 'report pending', however, the final audit report was issued on 05 December 2019.
- EM routine pharmacovigilance audit was not included in Annex G1 but was completed on 17 - 19 December 2019 and the report issued on 20 January 2020.
- [redacted] third party pharmacovigilance audit was not included in Annex G1 but was completed on 28 - 29 January 2020.

It is acknowledged that Annex G1 is updated bi-monthly, as detailed on the 'PSMF Call for Information' log. However, on request from a national competent authority (NCA), an accurate PSMF that reflects the current system in place should be provided.

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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]	

C.4.3 Minor findings

MI.1 Audit, deviation and CAPA management

Finding MI.1 a)
The following example of potential non-adherence to pharmacovigilance requirements that had not been sufficiently investigated by managerial staff was identified: In October 2019, a concern relating to the maintenance of the reference safety information in the SmPCs for two nationally authorised French products [redacted] was raised by the French LSO via the EMEA RSO Summary Report. Their concern was that no safety revisions of the SmPCs had been performed since the Eisai marketing authorisation transfer in July 2002, and as such, there was potential that the SmPCs may not be in line with the currently available scientific knowledge. At the time of the inspection, there had been no formal documented investigation by managerial staff into these concerns or any corrective, preventive and escalation action taken as necessary. As per GVP I.B.6. *"For the purpose of a systematic approach towards quality in accordance with the quality cycle, 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, preventative and escalation action as necessary"*
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 b)

One example of a deviation from a local procedure was identified [redacted] please refer to MA.2a) where it took 6 months between deviation identification and finalisation of the plan of actions to correct the deviation and prevent its recurrence.

[redacted] Handling deviations in the EMEA region' (04 July 2018) did not define a timeline for the management of unplanned deviations from local procedures, other than to report the deviation within one business day to the EEL pharmacovigilance compliance manager. To note, the timeline for managing unplanned deviations from corporate and regional procedures (as per [redacted] is a maximum of 13 days from deviation identification to the delivery of the approved deviation report to the CAPA responsible.

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)

Annex 1 of [redacted] Global Pharmacovigilance Audits' (12 June 2017) defined the timeframe for issuing final audit reports as within six weeks of the onsite audit, and the timeframe for issuing finalised CAPA plans as within 10 weeks of the onsite audit. Examples of failure to adhere to these procedural timelines were identified:

- Since January 2018, of the 22 audits listed in PSMF Annex G1, the reports for 10 of these were issued outside of six weeks, with delays of between three and 33 days.
- Included in these audits with delayed reports was the ESI routine pharmacovigilance audit conducted on 23 - 25 September 2019. The CAPA plan was finalised on 10 February 2020, over 19 weeks after the onsite audit. The CAPA plan only referenced the minor findings, not the one major finding identified, which was put 'on hold' with the reasoning given "*we may be able to obtain some more information about this topic through the MHRA inspection in February*". This is not an appropriate reason to delay CAPA implementation to resolve known non-compliance in the pharmacovigilance system.

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 MI.1 d)

The documented guidance for the risk assessment process undertaken to prepare the tactical pharmacovigilance audit plan was not considered to be appropriately detailed. The risk assessment was described in [redacted] 'Global Pharmacovigilance Audits' (12 June 2017) and [redacted] Managing Questionnaires used in Determining Risks for the Purpose of Developing Global Pharmacovigilance Audits Plans' (03 September 2019).

In order to generate the tactical pharmacovigilance audit plan, risk assessment questionnaires sent to RSOs and LSOs (who completed questionnaires on behalf of third parties) were scored to generate numerical outputs, and further qualitative factors were considered.

However, the working procedures did not include clear guidance on how entities would be selected for audit based on the interpretation of the numerical outputs and qualitative factors, hence it would not be possible to ensure that a consistent approach was being followed when selecting entities for audit.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MI.1 e)

Section 1.3 of [redacted] 'CAPA Management' (28 November 2019) stated that a CAPA tracker was used to detail all outstanding CAPAs, to include their status and any useful information. However, the MAH was not following this documented procedure, and during the inspection, it was confirmed that the CAPA tracker had not been maintained or in use since 2018. At the time of the inspection, the MAH did not have a documented system in place to track CAPA deliverables.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

MI.2 Post-authorisation safety studies (PASS)

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Finding MI.2 a)
There were no quality system documents that described how Eisai maintained oversight of non-interventional studies, in terms of protocol adherence and collection and reporting of AE/SAEs from such studies. It was noted for the [redacted] study that certain oversight measures were in place in the form of remote and onsite monitoring visits, safety data reconciliation, and query management, which were managed by a contract research organisation (CRO). The third-party CRO, AMS, was included in the audit risk assessment*. The company is reminded that the conduct of non-interventional studies, including PASS, form part of the critical pharmacovigilance processes referenced in [redacted] and as such the company should formally define how study oversight will be achieved, particularly for studies imposed as an obligation by EU NCAs and/or the MHRA. *In the third-party risk assessment questionnaire, when asking what types of activities were delegated to the company, the weighting for study data management was considerably lower compared with patient support programme (PSP) providers, compassionate use programme management and market research vendors (1 point vs. 10 points).
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]

[redacted]	

Finding MI.2 b)

The interim study report for the [redacted] study, dated 15 November 2019, had not been uploaded to the EU PAS Register.

GVP Module VIII.B.2 states *"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)."*

[redacted] 'The Corporate SOP for Post Authorization Safety Study' (14 June 2018) did not include the requirement to upload study results to the EU PAS Register.

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 MI.2 c)

[redacted] The Corporate SOP for Post Authorization Safety Study' (14 June 2018) stated that the EU QPPV was responsible for the following:

- *"Receives all new and amended study protocols (or synopses in English when there is no English protocol available) directly either from the Protocol Review Committee (PRC) or from Japan Asia PV department (JAPV). The latter for studies to be conducted in Japan.*
- *Reviews the above protocols or synopses in order to make a determination on whether a post authorization study is a PASS or not."*

However, [redacted] 'Develop, Approve and Maintain Clinical Study Protocol and Informed Consent Documents' (22 August 2018) did not include any reference to sending protocols to the EU QPPV for the PASS determination.

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]
[redacted]

MI.3 Collection and collation of safety data

Finding MI.3 a)
There was no evidence of a signed adverse event reporting agreement with the PSP vendor, 'Patients & Purpose'. The agreement was re-signed by the relevant parties on 18 February 2020, during the inspection. This vendor was supporting a programme entitled [redacted] and Living With LGS', which started in August 2013 and was ongoing at the time of the inspection. Eisai is requested to consider whether ongoing reconciliation of events has occurred with the vendor and whether adverse event reports have been received by the vendor.
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]	

Finding MI.3 b)
The EMEA RSO conducted a monthly reconciliation with third parties as per the relevant SDEA to ensure that all adverse event reports had been received. Reconciliation covering April 2019 was initiated on 10 May 2019; however, no response was received from distributors in South Africa [redacted] and Bosnia & Herzegovina [redacted] [redacted] PV Third Party Reconciliation' (13 March 2019) stated in section 1.8 'Reconciliation tracker' that "*If responses are not received within 7 calendar days a follow up email is sent. The date the follow up email was sent is also noted on the tracker as are any actions taken in respect to issue escalation.*" However, no further action had been taken by the MAH.

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In addition, the status of reconciliations in May 2019 had not been documented in the tracker in accordance with [redacted] for 13 other partners despite reconciliation being complete.

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.3 c)

One example of where a medical information specialist did not follow company procedures to clarify potentially reportable events with an enquirer was identified.

A UK medical enquiry [redacted] was received on 17 January 2019 from a pharmacist querying the administration of [redacted] in the evenings, as per SmPC section 4.2. The pharmacist stated that the patient struggled to remember to take their evening dose.

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However, the enquiry handler did not ask the pharmacist whether the patient had missed any doses. The ESMS working instruction, 'Instructions for Eisai Europe Ltd: Provision of Medical Information Services on behalf of Eisai' [redacted] 13 May 2019), defined 'missed doses' as an adverse event in section 6.1 'Definitions' and stated that these should be reported.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

MI.4 Processing of AEs and ADRs

Finding MI.4 a)

Over 100 invalid reports lacking a patient identifier and over 40 invalid reports lacking an adverse event were identified that had been incorrectly assigned the category 'Adverse event' rather than the category 'Inquiry/Invalid' on the safety database.

The Coding Manual for Global Product Safety Surveillance System (dated 28 May 2019), section 5.6.1 'Invalid' stated: *"Reports that are missing specific elements and therefore cannot be validated as true adverse event reports will be placed in the Invalid track […]*

The activities to be completed by the user in this track are as follows:

• ***Confirm Invalid*** *– User confirms that the case is invalid. If confirmed invalid, complete the activity and move case to the next step. If the case is valid, then the case is aborted and should be placed into the appropriate track."*

The default category for reports entered into the safety database was 'Adverse event' and

required manual amendment by the case processor, if applicable, in line with the guidance stated above.

To note, these reports had not been incorrectly reported to EudraVigilance, nor included in signal detection outputs. The MAH confirmed that invalid reports without an adverse event had not been incorrectly included in a PSUR, however, the MAH should confirm whether other invalid reports (i.e. those missing patient identifiers) had been incorrectly included, and if so, assess the impact of this on conclusions made in PSURs.

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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]	

[redacted]

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[redacted]

MI.5 Periodic safety update reports (PSURs)

Finding MI.5 a)
The [redacted] PSUR covering 13 February 2018 – 12 February 2019 (dated 08 April 2019) was reviewed during the inspection, and the following errors and incomplete calculation of exposure figures were identified: • A consistent approach was not applied for the inclusion of sales data in the calculation of exposure figures within PSUR interval periods. For 11 of the 39 regions, sales data had been included for February 2018 and February 2019, however for the remaining regions, data had not been included for February 2019. • USA sales data for March 2018 were not supplied to the authors when calculating exposure figures, resulting in [redacted] of product not being included within the cumulative or interval calculations (USA figures showed [redacted] distributed in the interval as opposed to [redacted] a difference of ~7% for the territory). • Two transcribing errors were identified in Table 1 of Appendix 6 [redacted] Patient Exposure' relating to the total number of mg distributed for the interval: - India: the figure showed a distribution of [redacted] rather than [redacted] To note, the correct figure had been used to calculate the cumulative total for all countries, and hence did not impact the total mg distributed in the interval. - Singapore: the figure showed a distribution of [redacted] whereas the sales data showed a distribution of [redacted]
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]	

MI.6 Signal management

Finding MI.6 a)
Documented signal detection methodology lacked sufficient detail with regard to the review of EudraVigilance signal detection outputs (eRMRs). Eisai had one substance, [redacted] included in the pilot on signal detection in EudraVigilance. [redacted] 'Corporate SOP for the Signal Management' (01 January 2019) and [redacted] 'EMEA Region Working Practice for Signal Management' (02 January 2019) outlined the process at a high-level and advised what would be considered a signal that required validation: "*The GSO reviews the eRMR, including the information on any signals of disproportionate reporting, to identify any potential signals that require validation and/or further assessment. Validation of any potential signals from this source includes review of the available Line Listings (LL) for the event(s) in EudraVigilance.*" However, several steps were undertaken prior to the GSO review. These included filtering the 'New Serious' column to remove all events that did not have a new, serious case in the reporting interval, and filtering again on the 'SDR all' column to identify any events that met the SDR threshold. An initial assessment was then conducted to remove listed and previously assessed events, leaving a final subset of cases to be reviewed by the GSO.
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]

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

Finding MI.6 b)
There was incomplete tracking of the signal concerning hypoglycaemia with [redacted]. No preliminary assessment/validation outcome or corresponding date was entered in the tracker, despite the signal having been through a validation and subsequently closed.

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]	

MI.7 Maintenance of EU risk management plans (RMPs)

Finding MI.7 a)

The following non-compliance was identified with regards to EU RMP maintenance:

- [redacted] EU RMP ([redacted] 11 March 2016) Part III included an outstanding action in relation to study [redacted] (Completion and evaluation of [redacted] in Patients with Refractory Partial Seizures Uncontrolled with Other Anti-Epileptic Drugs) and the status was shown as 'ongoing'. However, Eisai confirmed that study [redacted] was completed in 2017.

  As per GVP V.C.2.1. *"An RMP update is expected to be submitted at any time when there is […] a new or a significant change in the existing additional pharmacovigilance […] activities. The significant changes of the existing additional pharmacovigilance […] activities may include removing such activities from the RMP."*

- The [redacted] EU RMP ([redacted] 11 March 2016) and [redacted] EU RMP (version 11.2, 28 April 2014) did not include targeted follow-up questionnaires. Targeted questionnaires had been used for reports of aggression and suicidal behaviour with [redacted] since 29 January 2014, and for a range of conditions reported in children and adolescents with [redacted] since 14 June 2017.

  It is acknowledged that an updated [redacted] (version 4.3), which included the targeted follow-up questionnaires in Annex 4 'Specific Adverse Drug Reaction Follow-Up Forms', was submitted to the EMA in Autumn 2019, and at the time of the inspection was undergoing assessment.

  As per GVP V.B.6.1.1. *"Where an applicant/marketing authorisation holder is requested,*

or plans, to use specific questionnaires to obtain structured information on reported suspected adverse reactions of special interest, the use of these materials should be described in the routine pharmacovigilance activities section and copies of these forms should be provided in RMP annex 4."

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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]

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

C.4.4 Comments

1. Signal detection

The numerical threshold applied to identify signals for newer products may not be appropriate for all products. [redacted] 'Corporate SOP for the Signal Management' (01 January 2019) stated:

"*Additional numerical thresholds that will trigger a review of individual ICSRs to determine if there is a potential signal include:*

• *3 or more reports of any serious unlisted reactions in a rolling 3-month period for a product for the first 5 years after launch of a product.*"

Although none of the products in the portfolio at the time of inspection were within five years from product launch, the total events received per month for most products was low and therefore this threshold is unlikely to ever be met. It was noted however that this numerical threshold was being applied alongside a qualitative analysis and reviews of frequencies in intervals (monthly and three monthly) against the cumulative data.

As per GXP IX.B.2. "*Signal detection should follow a methodology which takes into account the nature of data and the characteristics*".

2. Medical information enquiries

In the standard response documents for [redacted] the references included a link to the SmPC for the tablet formulation on the eMC, but not to the oral solution. UK [redacted] was launched in 2019 (wholesaler availability, March 2019; pharmacy availability April 2019). For full transparency, it is recommended that the references are updated to include a link to both formulations.

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 as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 10555/830938-0015	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Eisai	**DATE**	17 February 2020
LOCATION	Eisai, Mosquito Way, Hatfield, AL10 9SN	**START TIME**	9.00am for 9.30am 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 *(approx. 20 minutes)*	BW	All welcome
Receipt and review of documentation		Inspectors only
LUNCH	-	-
Spontaneous sources of safety data To include: • License and distribution agreements • Medical information and product quality complaints • Literature	SR	[redacted]

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Solicited sources of safety data To include: • Non-interventional studies, including PASS • Patient support programmes • Market research programmes	KT	[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 10555/830938-0015	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Eisai	**DATE**	18 February 2020
LOCATION	Eisai, Mosquito Way, Hatfield, AL10 9SN	**START TIME**	09:00am

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Quality management system To include: • CAPA management • Deviation management • Pharmacovigilance audit • Compliance monitoring	BW	[redacted]
LUNCH	-	-

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Signal management To include: • Signal detection, validation, evaluation and actions (up to submission of variations) • Tracking and quality assurance	RL	[redacted]
Management of ICSRs To include: • Data entry and case assessments • Submission to EudraVigilance • Follow-up activities	SR	[redacted]

MHRA INSPECTION NUMBER	Insp GPvP 10555/830938-0015	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Eisai	**DATE**	19 February 2020
LOCATION	Eisai, Mosquito Way, Hatfield, AL10 9SN	**START TIME**	09:00am
Purpose of Interview	**Session Lead**	**Staff to be interviewed**	

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~~***Periodic Safety Update Reports (PSURs)***~~ *No specific interview session held on the topic of PSURs – reviewed by document request only*	RL	[redacted]
Document review	-	Inspectors only
LUNCH	-	-
Document review	-	Inspectors only

MHRA INSPECTION NUMBER	Insp GPvP 10555/830938-0015	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Eisai	**DATE**	20 February 2020
LOCATION	Eisai, Mosquito Way, Hatfield, AL10 9SN	**START TIME**	09.00am

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Ad-hoc questions and queries	-	-
Document review	-	Inspectors only
LUNCH	-	-
Inspector meeting	-	Inspectors only
Closing Meeting		All welcome

N.B. Documents will be requested during the inspection. This inspection plan may need to be amended during the inspection. Some interview sessions may be held in parallel.
Inspectors: [redacted]