Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

# PHARMACOVIGILANCE INSPECTION REPORT

**Pharmacovigilance System Name:** AstraZeneca UK Limited

**MHRA Inspection Number:** Insp GPvP 17901/31196-0006

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 |
| AZ | AstraZeneca |
| CAP | Centrally Authorised Product |
| CAPA | Corrective and Preventative Action |
| CHMP | Committee for Medicinal Products for Human Use |
| CRO | Contract Research Organisation |
| DHPC | Direct Healthcare Professional Communication |
| EMA | European Medicines Agency |
| EU | European Union |
| FPFV | First patient, first visit |
| GVP | Good Vigilance Practice |
| ICH | International Conference on Harmonisation |
| ICSR | Individual Case Safety Report |
| LPLV | Last patient, last visit |
| MAH | Marketing Authorisation Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MedI | MedImmune |
| NAP | Nationally Authorised Product |
| NIS | Non-Interventional Study |
| PASS | Post-Authorisation Safety Study |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PSMF | Pharmacovigilance System Master File |
| PSUR | Periodic Safety Update Report |
| PV | Pharmacovigilance |
| QPPV | Qualified Person responsible for Pharmacovigilance |
| RMP | Risk Management Plan |
| SAE | Serious Adverse Event |
| UK | United Kingdom |

## SECTION A: INSPECTION REPORT SUMMARY

Section 40 & 43

| | |
|---|---|
| **Inspection type:** | Statutory National Inspection |
| **System(s) inspected:** | AstraZeneca UK Limited [redacted] |
| **Site(s) of inspection:** | AstraZeneca UK Ltd<br>600 Capability Green<br>Luton<br>Bedfordshire<br>LU1 3LU |
| **Main site contact:** | [redacted]<br>Pepparedsleden 1<br>431 83 Mölndal<br>Sweden<br><br>[redacted] |
| **Date(s) of inspection:** | 11 – 14 November 2019 |
| **Lead Inspector:** | [redacted] |
| **Accompanying Inspector(s):** | |
| **Previous inspection date(s):** | 15 – 18 October 2013 & 28 – 30 October 2013;<br>29 November – 03 December 2010;<br>17 – 21 September 2007;<br>28 July – 01 August 2003 |
| **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, ADR reports were examined for all CAPs and UK NAPs. Specific PSURs were examined for [redacted] |
| **Name and location of EU QPPV:** | [redacted]<br>Pepparedsleden 1<br>431 83 Mölndal<br>Sweden<br><br>[redacted] |
| **Global PV database (in use at the time of the inspection):** | Sapphire version 5.5.0 (bespoke) |
| **Key service provider(s):** | Case processing, signal detection and document management for the production of periodic reports for all products provided by Tata Consultancy Services.<br>UK medical information services provided by PrimeVigilance. |
| **Inspection finding summary:** | 0 Critical findings<br>3 Major findings<br>3 Minor findings |
| **Date of first issue of report to MAH:** | 06 January 2020 |
| **Deadline for submission of responses by MAH:** | 10 February 2020<br>25 March 2020 |
| **Date(s) of receipt of responses from MAH:** | 07 February 2020<br>25 March 2020 |

| | |
|---|---|
| | 03 April 2020 |
| **Date of final version of report:** | 17 April 2020 |
| **Report author:** | [redacted] |

## SECTION B: BACKGROUND AND SCOPE

### B.1 Background information

AstraZeneca UK 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 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.

AstraZeneca UK Limited is a marketing company of AstraZeneca which operates globally in more than 100 countries. Pharmacovigilance activities are carried out globally at seven AstraZeneca sites: Cambridge, UK; Gaithersburg, Waltham and San Francisco, USA; Gothenburg, Sweden; Bangalore; India and Barcelona, Spain.

Case handling for all products and some routine safety surveillance activities, including signal detection for marketed products and document management for production of periodic reports for all products, have been outsourced to Tata Consultancy Services (TCS) operating from India and Hungary. UK medical information services are provided by PrimeVigilance.

AstraZeneca's product portfolio consists of CAPs and NAPs in three main therapy areas:

- Respiratory and autoimmunity diseases,
- Cardiovascular and metabolic diseases,
- Oncology.

In addition, AstraZeneca also held marketing authorisation for products for use in gastrointestinal diseases, neuropsychiatric diseases and vaccines.

At the time of the inspection, the PSMF was located in Sweden, therefore the Swedish Medical Products Agency (MPA) was the Supervisory Authority responsible for conducting pharmacovigilance inspections on behalf of the EMA.

### B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance systems and was performed at AstraZeneca's offices in Luton, Bedfordshire. Personnel from AstraZeneca attended the Luton site or were available via teleconference in order to participate in 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).

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

### B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 05 September 2019) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection. The detail of these requests is contained within document request sheet A and B.

### 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 AstraZeneca offices, Luton on 14 November 2019.

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

## SECTION C: INSPECTION FINDINGS

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

Since the previous inspection in 2013 the company had made the following changes to the pharmacovigilance system:

Section 43

- The EU QPPV changed to [redacted] in 2015.
- ArisGlobal LifeSphere Signal and Risk Management System replaced the previously used Signal Management System in September 2018.

### 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**<br>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**<br>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)**<br>Detail the action(s) taken / proposed to correct the identified deficiency. |
| **Preventative Action(s)**<br>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)**<br>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)**<br>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 Reactions

**Requirements:**

**GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)**
VI.B.2. Validation of reports
"*Four minimum criteria are required for ICSRs validation: […]*
*d. one or more suspected adverse reaction*
*(see VI.A.1.1. for definition). If the primary source has made an explicit statement that a causal relationship between the medicinal product and the reported adverse event has been excluded and the notified competent authority or marketing authorisation holder agrees with this assessment, the report does not qualify as a valid ICSR since the minimum information for validation is incomplete (there is no suspected adverse reaction). […]*

*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.3. Follow-up of reports
"*When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases.*"

VI.B.5. Quality management
"*Correct data entry, including the appropriate use of terminologies (see VI.B.8. for ICSRs content and format), should be quality controlled, either systematically or by regular random evaluation.*"

**CPMP/ICH/377/95: E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting**
2. Definitions and Terminology Associated with Clinical Safety Experience, B. Serious Adverse Event or Adverse Drug Reaction
"*A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:*
- *results in death,*
- *is life-threatening, […]*
- *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
- *results in persistent or significant disability/incapacity, or*
- *is a congenital anomaly/birth defect."*

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

| **Finding MA.1 a)** |
|---|
| AstraZeneca had incorrectly submitted cases reporting the outcome of death only with no further information to EudraVigilance. Examples included: |

Section 43

- [redacted] was a spontaneous case received from a business partner in Canada on 21 February 2019 reporting the death of a patient who had used [redacted] with no further information provided. AstraZeneca physicians stated that they could not rule out the cause of death being related to [redacted], and therefore the case was sent to EudraVigilance on 04 March 2019.

- [redacted] was a spontaneous case received from a business partner in the US on 25 April 2019 reporting the death of a patient taking [redacted]. The patient's daughter had called a pharmacy to cancel the prescription as her mother had passed away. No further information was provided. AstraZeneca physicians stated they could not rule out the cause of death being related to [redacted] so the case was sent to EudraVigilance on 06 May 2019.

A review of the line listing of adverse event reports extracted from the safety database which was provided to inspectors for the purposes of the inspection and went back for three years, suggested there were up to [redacted] cases which only had the MedDRA PT "death" as a reported event and which had been submitted to EudraVigilance.

**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

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

**Preventative Action(s)**

[redacted]

Section 43

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

**Finding MA.1 b)**

The following deficiencies were identified in relation to case processing.

i. Cases were identified for which non-conservative seriousness assessments were made.

- [redacted] was a spontaneous case from the US from a Facebook post in which the reporter claimed that [redacted] "assists in causing dementia" and that it had happened to her mother. Dementia was coded as a suspected adverse event in the case but was coded as non-serious.

- [redacted] was a spontaneous case from the US originally received as a product quality complaint that described a caregiver being unsure whether she was administering the dose from the [redacted] to her autistic son.

  The term autism spectrum disorder had been coded as a non-serious suspected adverse drug reaction.

  It is questionable whether autism should have been coded as a suspect reaction, given the nature of the enquiry. However, if it was decided to code autism spectrum disorder as an event, then it should be considered serious, as the details in the case "because consumer is autistic and unable to provide feedback" met the [redacted] definition of "significant disability/incapacity".

- [redacted] was a spontaneous case for [redacted] rom the US and was created from three posts from a user on twitter. The case created in the safety database for these posts included two coded suspected reactions, brain neoplasm and drug ineffective which were both coded as non-serious.

  On review of the twitter posts, there was insufficient detail to ascertain whether the patient had a brain neoplasm, as only a hashtag of "#BrainTumorThursday" had been included at the end of a post.

  It is questionable whether brain neoplasm should have been coded as a suspected adverse reaction, but if it was decided the report was suggesting [redacted] had caused the brain neoplasm, this should have been coded as a serious event.

ii. [redacted] was a solicited case from the US which included an incorrectly coded event. The MedDRA PT "Bone Cancer" was coded as an event, even though the source information stated that the reported bone cancer was a concurrent disease.

iii. A small number of discrepancies in case types were identified from the line listing provided to the inspection team. The MAH confirmed the following errors:

[redacted]

Section 43

[redacted]

**Post-inspection request**: As part of the further assessment, the MAH should also comment on the impact on the correct presentation of these cases in PBRERs or other aggregate reports.

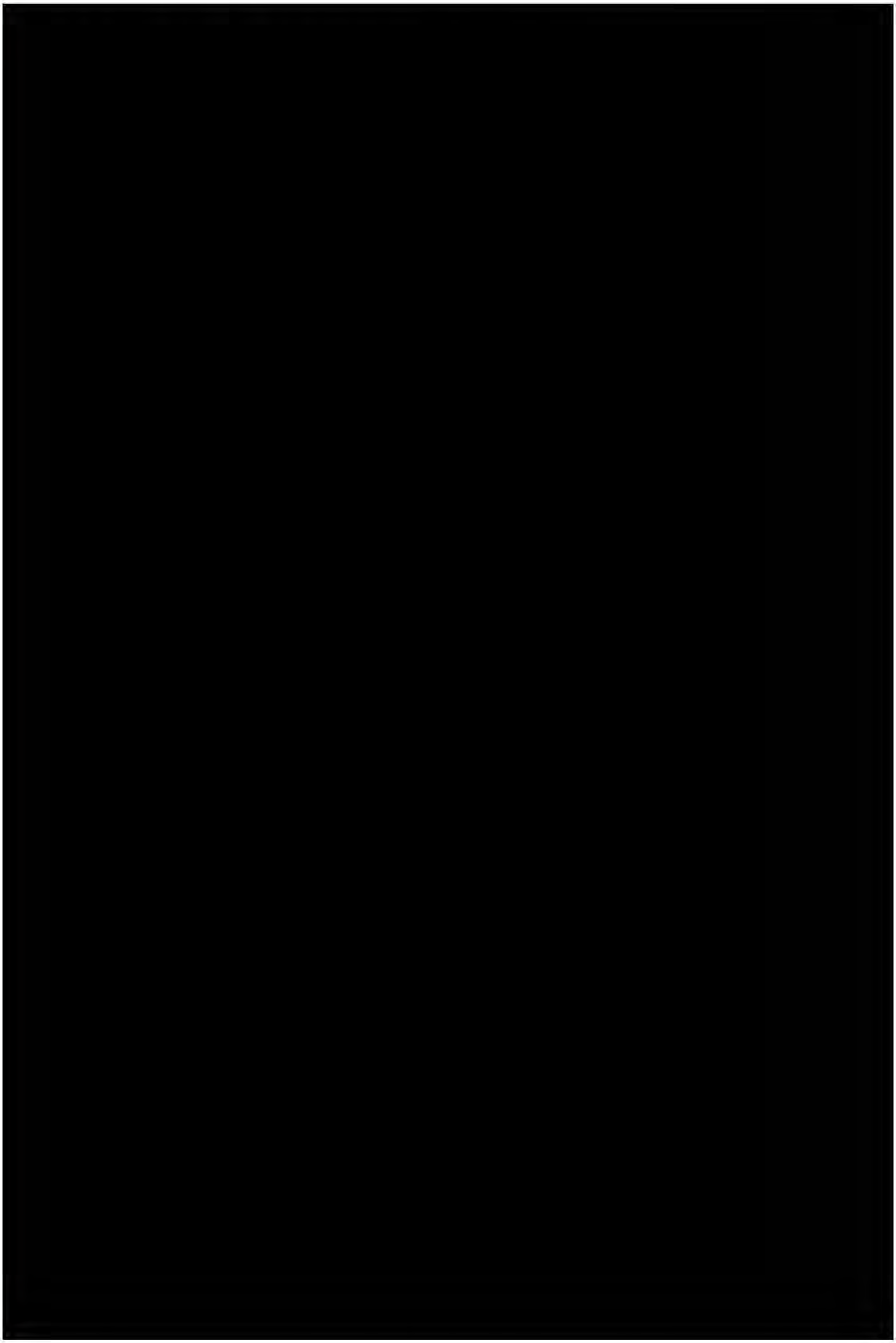
**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

Section 43



Section 43

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

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

**Finding MA.1 c)**

The following deficiencies were identified in relation to the request for follow-up information of adverse event reports.

i. There was a case for which no follow-up was conducted to obtain further information on the suspected drug reaction.

Case [redacted] was a spontaneous case received from the US by a parent who stated her son was autistic and was seeking access to [redacted] Her son had the drug previously as he did not "do well" with injections.

Autism spectrum disorder had been coded in this case as a non-serious suspected adverse drug reaction and the case evaluator stated that "No follow-up will be requested".

It is questionable whether autism spectrum disorder should have been coded as a suspected drug reaction. If the case was unclear, AstraZeneca should have followed up with the reporter to understand further details to assist in collecting correct and meaningful information.

ii. There was one case for which the request for follow-up information was sent to the reporter with a delay of six months.

Section 43

Case [redacted] was a spontaneous, serious case from the US of ketoacidosis with the use of Qtern (saxagliptin and dapagliflozin) reported by a healthcare professional to a sales representative on 15 January 2019. The case was submitted to pharmacovigilance on 25 February 2019; however, follow-up requests, which included the targeted questionnaire for ketoacidosis as required by the Qtern EU RMP [redacted], date of final sign off 07 December 2017), were only sent on 09 September 2019, 19 September 2019 and 29 September 2019 to the reporter.

[redacted] *Collection and Follow-up of Individual Case Safety Reports during Post-Marketing* [redacted] date effective 07 September 2017) stated "All follow-up attempts should be completed within 30 days of receipt of the case subject to the availability of the reporter."

**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

Section 43

[redacted]

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

| Preventative Action(s) |
|---|
| [redacted] |

| Deliverable(s) | |
|---|---|
| [redacted] | |

## MA.2 Signal Management

**Requirements:**

**GVP Module IX – Signal management (Rev 1)**
IX.B.5. Quality requirements
"*Through a tracking system, all organisations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.*"

**GVP Product- or Population-Specific Considerations II: Biological medicinal products**
P.II.B.4. Signal management
"*Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological and important differences between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change).*"

"*Denominator data and data of suspected adverse reactions (see GVP Module IX) should be analysed to support continuous signal detection and particularly detection of any apparent changes in suspected adverse reaction reporting rates or trends that could indicate new signals (particularly following manufacturing changes).*"

MAHs are obliged to ensure that information on the benefits and risks of their products is evaluated on an ongoing basis and appropriate action is taken in response to new information that impacts on the benefit-risk balance. The following findings were noted in relation to signal management:

Section 43

**Finding MA.2 a)**

AstraZeneca held marketing authorisations for the two biological medicines [redacted] The requirements for MAHs of biological medicines for signal management activities had not been met as there was no mechanism in place to monitor denominator data (exposure information) and data of suspected adverse reactions to support the detection of any apparent changes in suspected adverse reaction reporting rates or trends that could indicate new signals in line with the guidance in GVP PII.

[redacted] *Lot Analysis For Biologic Product Adverse Event Reports* [redacted] date effective 24 April 2016) stated that an annual lot analysis should be conducted which considered lot distribution information and reviewed safety information for increased adverse event frequencies in relation to specific batches; however, these reports were not produced.

It is acknowledged that a monthly lot analysis was conducted to review if any trends of ADRs were associated with specific batches in the previous month; however, this information was not evaluated in the context of batch-specific exposure information and only included reports for which at least one batch number had been reported.

**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 MA.2 b)**

Signals were tracked in the Next-Generation Signal Management System [redacted]. The following examples of potential signals were identified for which no priority was assigned in the signal tracker and the status did not reflect the actual status of the signals. The prioritisation category determined the time frame for validating the signal.

- Drug hypersensitivity with [redacted] detected 05 July 2019
- Myasthenia gravis with [redacted], detected 04 July 2019
- Immune thrombocytopenic purpura with [redacted] detected 10 June 2019 and 05 July 2019

According to the signal tracker these potential signals were in the further evaluation step to validate the signal at the time of the inspection. Review of supporting documentation showed that the potential signals had already undergone further assessment and were either non-valid or confirmed at the time of inspection.

**Root Cause Analysis**

[redacted]

Section 43

[redacted]

| Further Assessment |
| --- |
| [redacted] |

| Corrective Action(s) |
| --- |
| [redacted] |

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

Section 43

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

## MA.3 Pharmacovigilance Systems Masterfile

**Requirements:**

**Commission Implementing Regulation (EU) No. 520/2012**, Article 3(3) and Article 6(2)

**GVP Module II – Pharmacovigilance system master file (Rev 2)**
II.B. Structures and processes
"*The content of the PSMF should reflect global availability of safety information for medicinal products authorised in the EU, presenting information on the pharmacovigilance system applied at global, regional and local levels.*"

II.B.4.2 PSMF section on the organisational structure of the marketing authorisation holder
"*Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories. […] Individual contractual agreements shall be made available at the request of national competent authorities and the Agency or during inspection and audit and the list provided in the Annexes (see II.B.4.8.).*" (emphasis added)

II.B.4.8. Annex to the PSMF
"*A list of contractual agreements covering delegated activities including the medicinal products and territory(ies) concerned in accordance with Article 6(2) of Commission Implementing Regulation (EU) No 520/2012 (see II.B.4.3.) [IR Art 3(3)]; […].*" (emphasis added)

Every MAH should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorised medicinal products. Details of the system should be recorded in a PSMF, which should be permanently available for inspection. The following finding was noted in relation to the PSMF:

**Finding MA.3**

PMSF Annex B1 *Global Safety Agreements where AstraZeneca or MedImmune is the Licenser* (dated 03 September 2019) was not specific to EU-authorised products and did not include all required information.

i. Annex B1 included details of contracts with partners for unauthorised products (i.e. products still in clinical development) and products which were authorised in other territories, but not in the EU.

   As an example, the annex included the contract with AbbVie regarding [redacted] for which AstraZeneca only held rights to the product in the US, but AbbVie held the rights elsewhere globally, including the EU, and was responsible for pharmacovigilance activities in these territories.

ii. Annex B1 contained incomplete information on the territories in which pharmacovigilance responsibilities were delegated to partners.

   - The details of the agreement between AstraZeneca and Pfizer for fulvestrant and the fulvestrant/palbociclib combination therapy outlined the AstraZeneca territories as "all".

Section 43

Section 43

- The details of the agreement between AstraZeneca and Pfizer for [redacted], [redacted] and other products outlined the AstraZeneca territories as "Countries outside Pfizer territories" and the Pfizer territories as "See agreement for territories by product".

- The agreement between AstraZeneca and Takeda for [redacted] and other products outlined that the AstraZeneca territories were "exclusive rights in some countries e.g. USA & semi exclusive in other e.g. most European countries".

An overinclusive and incomplete Annex B impeded the inspectors' ability to ascertain where AstraZeneca had products on the market and where AstraZeneca had delegated its pharmacovigilance responsibilities in those territories.

**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

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

**Preventative Action(s)**

[redacted]

Section 43

[redacted]

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

## C.4.3 Minor findings

### MI.1 Periodic Safety Update Reports

Section 43

**Finding MI.1**

No exclusions based on causality were applied to the spontaneous cases for inclusion in the PBRER post-marketing summary tabulations. Per GVP Module VII section [redacted] *PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"* these are "cumulative and interval summary tabulations of adverse reactions" (emphasis added) and should not contain unrelated adverse events.

A review of [redacted] cases in the line listing exported from the safety database for the purposes of the inspection indicated that approximately [redacted] of spontaneous events were coded to unrelated in the safety database. A review of specific cases confirmed that the reporter had stated that the events were not related to [redacted] for example:

- [redacted] a spontaneous case received on 08 February 2019 from a physician with the events of fall, femur fracture and accident. The physician stated that "the event was unrelated to the drug because the event was accidental based on the fact that the patient tumbled which resulted in fall".

- [redacted], a spontaneous report received from a physician on 05 November 2018 for convulsion where the reporter stated that "The event was induced by not [redacted] but concomitant mental disease".

GVP Module VI section VI.A.1.1. *Adverse reaction, causality* states that "all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded." (emphasis added).

**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] | |

## MI.2 Additional Risk Minimisation Measures

| Finding MI.2 a) |
|---|
| The customer relationship management system Veeva that was used to record the distribution of UK educational materials by sales representatives did not reflect the actual distribution of the materials.<br><br>Three sales representatives had erroneously selected a drop down in the system which indicated the distribution of [redacted] educational materials. However, these sales representatives were Primary Care Account Specialists who should not have been distributing these materials as they had not received the relevant training.<br><br>There was no quality assurance or audit system in place for Veeva that would identify if sales representatives were distributing educational materials incorrectly or entering erroneous data into the customer relationship management system.<br><br>GVP Module XVI section XVI.B.3. *Implementation of risk minimisation measures* states that "Quality assurance mechanisms should ensure that the distribution systems in place are fit for purpose and auditable."<br><br>This finding was graded as minor as it was confirmed during the inspection that the educational materials had not been distributed by the sales representatives but that this had only been incorrectly recorded on the system. Therefore, there was no impact on patient safety. |
| **Root Cause Analysis** |
| [redacted] |
| **Further Assessment** |
| [redacted] |
| **Corrective Action(s)** |
| [redacted] |

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

| Preventative Action(s) |
|---|
| [redacted] |

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

| Finding MI.2 b) |
|---|
| There was no procedural documentation describing the review (and update as appropriate) of educational materials following safety updates to the product information. |

Section 43

It is acknowledged that none of the educational materials reviewed during the inspection contained out-of-date information or missed important information that was present in the product information.

**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

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

**Preventative Action(s)**

[redacted]

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

**Finding MI.2 c)**

The date stated in the educational materials did not match the MHRA approval date for the following products:

- [redacted] educational materials were approved by the MHRA on 05 April 2019; however, the materials (patient guide, patient alert card and physician brochure) were dated February 2019.
- The most recent version of the [redacted] educational materials were approved by the MHRA on 12 June 2018; however, the patient card was dated March 2018 and the healthcare professional guide was dated May 2018.

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

**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

Section 43

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

**Finding MI.2 d)**

The following deficiencies were identified in relation to the distribution of the DHPC letter for [redacted] (dated 08 May 2018) regarding possible medication errors with [redacted] tablet and capsule formulations.

i. The DHPC letter was disseminated approximately one week later than agreed in the MHRA-approved dissemination plan.

Under timelines for dissemination in the original submission by AstraZeneca to the MHRA, it was stated that "the DHPC Letter will be disseminated to the [...] audience approximately 1 week in advance of [redacted] tablets availability for private patients". The DHPC letter was approved by the MHRA on 08 May 2018, the launch date of [redacted] formulations was 10 May 2018 (date of arrival of stock in distribution centre) and the first date that prescribers could order [redacted] was 14 May 2018. However, DHPC letters were not mailed until 16 May 2018.

This finding has been graded as minor since the distribution of the letter was only two days after the tablet formulation was available to order and this is likely to have had no impact on patient safety.

ii. The MHRA-agreed dissemination plan referred to the postal distribution of the DHPC letter to UK oncology healthcare professionals. In addition to the mandated requirement, AstraZeneca uploaded a copy of the DHPC on the eMC website for the tablet formulations. However, the risk materials were not uploaded for the capsule formulation, despite being relevant to both formulations.

During the inspection, AstraZeneca also uploaded the DHPC on the eMC website for the [redacted] capsule formulation.

**Root Cause Analysis**

[redacted]

Section 43

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

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

**Preventative Action(s)**

[redacted]

Section 43

[redacted]

## MI.3 Oversight of Study Activities

Section 43

**Finding MI.3 a)**

[redacted]

**Root Cause Analysis**

[redacted]

Section 43

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

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

**Preventative Action(s)**

[redacted]

Section 43

[redacted]

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

**Finding MI.3 b)**

[redacted]

**Root Cause Analysis**

[redacted]

**Further Assessment**

[redacted]

**Corrective Action(s)**

[redacted]

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

Section 43

| [redacted] |
| --- |
| **Preventative Action(s)** |
| [redacted] |
| [redacted] |

## C.4.4 Comments

Section 43

1. [redacted]

2. A small number of cases were identified where the Key Ingredient field in the safety database was blank or incorrectly completed, for example:

   - For [redacted] cases closed between 01 January 2014 and 13 November 2019, 39 out of 13,879 drug-event pairs had a blank Key Ingredient field.

   - For [redacted] cases closed between 01 January 2014 and 13 November 2019, 10 out of 74,288 drug-event pairs were incorrectly coded with a key Ingredient of [redacted]

   The Key Ingredient field was manually populated from a drop-down list during data entry and was not linked to other suspect drug fields. The field was used to identify cases relevant for inclusion in the PBRER during a search in the Sapphire database.

   It is acknowledged that AstraZeneca had self-identified this deficiency during 2018 as recorded in Quality Issue [redacted], and a change to the [redacted] database was planned to be rolled out on 23 and 24 November 2019 (change request number: [redacted] so that the Key Ingredient field would be auto-populated based on the result of drug coding.

   Unless covered by the impending changes, it is expected that AstraZeneca consider whether any affected cases (including cases received prior to when AstraZeneca was global safety database holder) should be corrected to ensure any future cumulative PBRER and ad-hoc searches are complete.

3. The Safety Surveillance Plan (SSP) (dated 15 April 2019) for [redacted] did not reflect the actual frequency of signal detection activities. The SSP stated that routine signal detection would be carried out every four weeks; however, in practice this activity was carried out every two weeks. The MAH provided an addendum to the SSP specifying the increased frequency but the document was neither dated nor version controlled.

## 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).
- 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 17901/31196-0006 | **DAY** | 1 |
| **PHARMACOVIGILANCE INSPECTION OF** | AstraZeneca | **DATE** | 11 November 2019 |
| **LOCATION** | 600 Capability Green, Luton, Bedfordshire, LU1 3LU | **START TIME** | 09:00 arrival for 09:30 start |
| **Inspection team:** | [redacted] | | |
| **Purpose of Interview** | | **Staff to be interviewed** | |
| **Opening Meeting**<br>Review of scope of inspection and inspection plan<br><br>**Company Presentation**<br>Overview of the company, the pharmacovigilance system and the quality system. The presentation may also include information on any relevant ongoing remediation work in the pharmacovigilance system.<br>*(approx. 20 minutes)* | | [redacted] | |
| **Document collation and review** | | | |
| **LUNCH** | | | |

Section 40

Section 40

| | |
|---|---|
| **Collection and collation of safety data I**, including but not limited to<br>• Clinical trials, non-interventional studies incl. PASS, investigator-initiated studies<br>• Quality assurance and vendor oversight | [redacted] |
| ~~***Collection and collation of safety data II**, including but not limited to*~~<br>• ~~*Medical information*~~<br>• ~~*License agreements*~~<br>• ~~*UK Patient support programmes*~~<br>• ~~*Quality assurance and vendor oversight*~~ | [redacted] |
| N.B. The inspection plan may need to be amended during the inspection. | |

| | | | |
|---|---|---|---|
| **MHRA INSPECTION NUMBER** | Insp GPvP 17901/31196-0006 | **DAY** | 2 |
| **PHARMACOVIGILANCE INSPECTION OF** | AstraZeneca | **DATE** | 12 November 2019 |
| **LOCATION** | 600 Capability Green, Luton, Bedfordshire, LU1 3LU | **START TIME** | 09:00 |
| **Purpose of Interview** | | **Staff to be interviewed** | |
| **Additional risk minimisation measures**, including but not limited to<br>• Submission, maintenance and distribution of UK educational materials and DHPCs<br>• Effectiveness of risk minimisation measures | | [redacted] | |
| ***Collection and collation of safety data II,*** *including but not limited to*<br>• *Medical information*<br>• *License agreements*<br>• *UK Patient support programmes*<br>• *Quality assurance and vendor oversight* | | | |
| **LUNCH** | | | |

Section 40

Section 40

| | |
|---|---|
| **ICSR management**, including but not limited to<br>• Data entry, coding assessments and submission to EudraVigilance<br>• Follow-up activities<br>• Quality assurance and vendor oversight | [redacted] |
| **Signal detection and management**, including but not limited to<br>• Signal detection, validation, evaluation and tracking and consideration of requirements for biologicals<br>• Quality assurance and vendor oversight | |

| Section 40 | [redacted] |
| --- | --- |
| | Please note that the afternoon sessions may run in parallel. |

| | | | |
|---|---|---|---|
| **MHRA INSPECTION NUMBER** | Insp GPvP 17901/31196-0006 | **DAY** | 3 |
| **PHARMACOVIGILANCE INSPECTION OF** | AstraZeneca | **DATE** | 13 November 2019 |
| **LOCATION** | 600 Capability Green, Luton, Bedfordshire, LU1 3LU | **START TIME** | 09:00 |
| **Purpose of Interview** | | **Staff to be interviewed** | |
| **Periodic safety update reports** | | [redacted] | |

Section 40

Section 40

| | |
|---|---|
| | [redacted] |
| ***Ad-hoc session: Signal management for biologicals*** | |
| **LUNCH** | |
| ***Ad-hoc session: Sapphire*** | [redacted] |
| **Document review and ad-hoc questions** | As required |

| | | | |
|---|---|---|---|
| **MHRA INSPECTION NUMBER** | Insp GPvP 17901/31196-0006 | **DAY** | 4 |
| **PHARMACOVIGILANCE INSPECTION OF** | AstraZeneca | **DATE** | 14 November 2019 |
| **LOCATION** | 600 Capability Green, Luton, Bedfordshire, LU1 3LU | **START TIME** | 09:00 |
| **Purpose of Interview** | | **Staff to be interviewed** | |
| **Document review and ad-hoc questions** | | As required | |
| **LUNCH** | | | |
| **Closing meeting** | | All welcome | |