Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Ipsen

MHRA Inspection Number: Insp GPvP 34926/93052-0012

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
NIS	Non-Interventional Study
PBRER	Periodic Benefit Risk Evaluation Report
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory national re-inspection
System(s) inspected:	Ipsen, [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	One day of re-inspection conducted by [redacted] and [redacted] on 05 November 2019. Further re-inspection conducted over five non-consecutive days between 28 April and 12 June 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	03-06 September 2018 10-12 June 2014 26-28 October 2010 04-06 February 2008 29 June - 2 July 2004
Purpose of inspection:	Re-inspection to determine if appropriate action had been taken from the previous inspection and to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the review, the PSUR for CAP product [redacted] (DLP 31 August 2019) was examined.
Name and location of EU QPPV:	[redacted] contact details as above.
Global PV database (in use at the time of the inspection):	ARISg v 7.4.5.2 HF1 (Commercially available)
Key service provider(s):	Case processing services provided by Parexel.
Inspection finding summary:	03 Major findings 01 Minor finding
Date of first issue of report to MAH:	03 July 2020
Deadline for submission of responses by MAH:	06 August 2020
Date(s) of receipt of responses from MAH:	04 August 2020, 21 August 2020
Date of final version of report:	01 September 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Ipsen Biopharm Ltd (Ipsen) was selected for re-inspection as a result of two critical findings that were identified during the previous routine inspection of the MAH, performed on 03-06 September 2018. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the previous inspection. In addition, the inspection provided an opportunity to re-examine the overall compliance of the pharmacovigilance system 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.

Ipsen is a mid-sized biopharmaceutical company with a global presence. Ipsen has nine products in its portfolio that are authorised in the UK, which includes three centrally authorised products. The PSMF is located in France and therefore Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) are the supervisory authority responsible for conducting pharmacovigilance inspection on behalf of the EMA.

In 2018, after announcing the intention to conduct a pharmacovigilance inspection of Ipsen, the MHRA was notified by the MAH of a number of non-compliances that had been identified by Ipsen within the pharmacovigilance system. The MHRA inspection in 2018 subsequently reported two critical findings in the pharmacovigilance system (refer to section C.4.1.), and the MAH has been undergoing extensive remediation activities and business improvements since that time (refer to section C.1.).

B.2 Scope of the inspection

The inspection centred on reviews of data outputs from the global safety database and the data clean-up activities associated with the critical findings reported in 2018. The inspection was predominantly performed via document review; however, personnel involved in pharmacovigilance activities were available via videoconference throughout the inspection for ad-hoc queries. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

The operational pharmacovigilance activities and processes affected by the 2018 critical finding for the quality management system for pharmacovigilance were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

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B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] 31 December 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.

B.4 Conduct of the inspection

On 05 November 2019, a reinspection day was conducted by the Lead Inspector to assess progress with the 2018 CAPA. Due to the current COVID-19 pandemic, further re-inspection was performed entirely remotely over five non-consecutive days. In general, the inspection was performed in accordance with the Inspection Plan. A closing meeting was held to review the inspection findings via videoconference on 12 June 2020. A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

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

Since the previous inspection in 2018 Ipsen had implemented a Business Improvement Project (BIP) with workstreams across the patient safety organisation and associated quality management system. The BIP was completed and closed on 31 March 2020. The following changes had been implemented in the pharmacovigilance system:

- A new head of Global R&D Quality joined in May 2019.
- The safety organisation was restructured, safety governance was simplified and from early 2020, the Global Patient Safety organisation (GPS) reported to the Chief Medical Officer.
- GPS increased in size from 30 FTA to 52 FTE, with plans to further increase headcount in the coming year.
- A new labelling team and associated governance structure was implemented.
- An extensive data cleaning project was rolled-out to the data in the safety database in November 2019.
- The reporting tools [redacted] and Analytics were implemented to assist with extraction of data from the database using validated standard reports.

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In addition, the PSMF was relocated from UK to France on 22 February 2019.

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

In 2018, Ipsen was issued with two critical findings:

- CR.1 Quality management system for pharmacovigilance, relating to significant deficiencies observed in the management of known non-compliance in the pharmacovigilance system, mechanisms for compliance management across critical pharmacovigilance processes and written procedures for critical pharmacovigilance activities.
- CR.2 Provision of information for inspections, specifically the provision of incomplete and inaccurate data outputs from the safety database.

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During this remote re-inspection, the data clean-up activities completed since the 2018 inspection were reviewed, together with the [redacted] that was produced prior to the roll-out of the clean-up activities, in order to assess the impact of data corrections and the extent of changes to data already submitted to regulatory authorities.

At the time of this re-inspection, the critical finding for the provision of information for inspections is considered to be resolved.

The remediation of the 2018 critical finding for the quality management system was not fully assessed during this re-inspection, due to changes to the inspection scope and conduct brought about by the Covd-19 pandemic. Although inspectors did not identify indications that a critical issue remained for the quality management system, the complete resolution of the critical finding in this area should be verified at a subsequent inspection in the near future.

C.4.2 Major findings

MA.1 Periodic safety update reports

Requirements:

GVP Module VII (Rev 1)
VII.B.5.6.3. PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"

VII.B.6. Quality systems for PSURs at the level of marketing authorisation holders
"The provision of the data included in the summary tabulations (see VII.B.5.6.) should undergo source data verification against the marketing authorisation holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented."

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Finding MA.1 a)

Unrelated serious adverse events had been incorrectly included in the cumulative and interval tabulation 'Numbers of adverse drug reactions by preferred term from post-marketing sources' (Appendix 3) of the [redacted] (DLP 31 August 2019). A number of spontaneous case examples were identified where the reporter had explicitly stated that the event was not related to [redacted] and the company assessment had not diverged from this, yet these events had been included in counts of adverse reactions. These examples included:

i) [redacted] a UK spontaneous report received from a healthcare professional which reported the event preferred term (PT) 'Diabetic ketoacidosis'. Source information from the reporter stated "*The DKA was not an adverse reaction from the* [redacted]

ii) [redacted] a Polish spontaneous report received from a healthcare professional which reported the event PT 'Cardiac arrest'. The doctor reporting had stated the reaction was not related.

iii) [redacted], a German spontaneous report received from a healthcare professional which reported the event PT 'Cardiac failure'. The case source documentation stated, *"the physician sees no causal relationship with* [redacted] *therapy"*.

iv) [redacted] a spontaneous report received from a healthcare professional in the USA, which reported the event PT 'Intestinal neuronal dysplasia'. The case source documentation included the following statements: "*The underlying disease state, neuronal intestinal dysplasia type B causing pseudo-obstruction, caused the decreased ostomy output (rather than the drug)*".

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

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[redacted]

Preventative Action(s)

[redacted]

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

Finding MA.1 b)

An isolated example of a reaction missing from the cumulative data included in the post-marketing summary tabulation for the [redacted] (DLP 31 August 2019) was identified.

The reaction of drug-induced hepatitis, related to [redacted], was initially received as a solicited post-marketing report on 25 May 2011 [redacted] This serious ICSR was correctly submitted to the MHRA; however, the structured causality fields in the database were inadvertently modified to incorrectly classify the case as 'unrelated' during processing of the latest information received on 11 June 2011. As a result, this reaction was excluded from the cumulative summary tabulation in the PSUR.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)

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[redacted]

Preventative Action(s)

[redacted]

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

Finding MA.1 c)

At the time of submission of the [redacted] (DLP 31 August 2019, final report dated 30 October 2019), there was no evidence to support completion of a quality control (QC) check on the data used to compile the summary tabulations. Upon request during the MHRA reinspection day conducted on 05 November 2019, no evidence was provided, and confirmation of the completed quality check was conducted retrospectively in the form of a signed note to file.

In 2018 a major finding (MA.5, inspection reference Insp GPvP 34926/93052-0011) was issued for a lack of evidence to support the completion of QC on the data used to compile the PSUR summary tabulations, and that the process for this QC was not described in any written procedures. In response to this finding, written procedures were updated to include details of the required QC [redacted] Periodic Safety Update Report and Periodic Benefit Risk Evaluation Report', v9.0 effective 18 July 2019), which describes QC to be conducted on source data. Ipsen confirmed that this QC was carried out for the [redacted]; however, there had been a failure to properly document this QC.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.1 d)
It was identified that there were cases in the safety database that were assigned an incorrect case classification due to an error in capturing the primary source, for example:

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- 19 cases classified as spontaneous but coded as being reported from non-interventional study [redacted] (compared with 457 cases coded as being received from this study and were classified as solicited)
- Four cases reportedly received from clinical study [redacted] incorrectly classified as being from a solicited post-marketing source.

On identification of this issue by inspectors, Ipsen conducted a review of the 83 cases with an incorrect primary source that were identified during the inspection in the line listing C1 (all worldwide adverse event reports received for all EU/UK authorised products from 01 November 2016 to 21 February 2020). Ipsen identified that the errors have resulted in the incorrect inclusion/presentation of events in PSUR summary tabulations of serious adverse events from clinical trials and post-marketing adverse reactions for affected products.

Ipsen confirmed that for the data reviewed (back to 01 November 2016) there was no impact to expedited reporting.

Details of the PSURs affected and an assessment of the impact should be provided in the responses.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

MA.2 Management and reporting of ICSRs

Requirements:

GVP Module VI (Rev 2)
VI.A.1.1. Adverse reaction, causality

VI.B.2. Validation of reports

VI.C.2.2.3.2 Exclusion criteria for the submission of ICSRs published in the medical literature

During the inspection, the following examples of incorrect submissions to EudraVigilance and MHRA were identified.

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Finding MA.2 a)

Examples of post-marketing solicited and spontaneous reports were identified to have been incorrectly submitted to EudraVigilance or MHRA, where the reporter had explicitly stated that the event was unrelated to the company product, [redacted]

i) [redacted], a serious solicited report from France of 'Papillary thyroid cancer' and 'Off label use', received 09 October 2018 and first reported to EudraVigilance 22 October 2019. The reporter causality was stated as 'no reasonable possibility' for papillary thyroid cancer and 'not reported' for off label use and the company causality was assessed to be 'no reasonable possibility' for both events.

ii) [redacted], a serious solicited report of 'Malignant melanoma' and 'Off label use' from the USA, received 22 May 2012 and reported to the MHRA on 30 May 2012. The reporter causality was not provided for either event and the company causality was assessed as 'no reasonable possibility'.

iii) [redacted] a serious spontaneous report of 'Cardiac arrest' from Poland, received from a healthcare professional on 09 April 2019 and reported to EudraVigilance on 10 April 2019. The doctor reporting had stated the reaction was not related to [redacted]

iv) [redacted], a serious spontaneous report from the USA of 'Intestinal neuronal dysplasia', 'Condition aggravated' and 'Expired product administered', received from a healthcare professional on 26 February 2014 and reported to the MHRA on 12 March 2014. The case source documentation included the following statements from the reporter after clarifying that he was only calling to inquire about the use of expired [redacted] "*I cannot sign off on the attached document* [adverse event report] *because I do not think it is an accurate representation of this patient case. The underlying disease state, neuronal intestinal dysplasia type B causing pseudo-obstruction, caused the decreased ostomy output (rather than the drug)*".

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

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

Finding MA.2 b)
Seven serious ICSRs identified from a literature article were incorrectly coded as Ipsen branded products and erroneously submitted to EudraVigilance as cases from a post-marketing solicited source. A literature article dated 1998 was received by Ipsen on 20 May 2019 concerning recombinant human insulin-like growth factor-[redacted] and recombinant human growth hormone (GH). The article did not reference the brand name of either product, however Ipsen entered ten reports (seven serious; three non-serious) from the article into the global safety database, classifying the reports as from post-marketing sources and coding the suspect products as the Ipsen brands, [redacted] and [redacted] At the time of publishing (1998), Ipsen had not commercialised either of the suspect medicinal products in the country of origin. Therefore, as ownership of the suspected medicinal products could be excluded, there was no requirement for the submission of ICSRs to the post-marketing module of EudraVigilance. Ipsen is reminded that the requirement to search the literature starts on submission of a marketing authorisation application and responsibilities apply to reports related to medicinal products for which ownership cannot be excluded.
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]	

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Finding MA.2 c)

One report was identified that had been incorrectly submitted to EudraVigilance despite not meeting the minimum reporting criteria. The case reported the outcome of death only with no further information provided.

- Case [redacted] a spontaneous report from the UK reported to Ipsen through social media, was received 24 May 2019 and reported to EudraVigilance 31 May 2019

In addition, the source information did not clearly indicate that the report related to [redacted] The report was first identified from a news article that referred only to [redacted]. A subsequent post on Twitter from an unrelated healthcare professional suggested that the news article may refer to an [redacted] effect. It is recognised that a conservative approach has been taken; however, the case narrative with regards to the relationship with [redacted] was misleading. Although at the end of the narrative it stated, "*It was not confirmed whether the patient received* [redacted] initial statements within the narrative submitted to EudraVigilance included "*The case concerns a 14-year old female patient who died while on treatment with* [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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

MA.3 The pharmacovigilance system master file

Requirements:

GVP Module II (Rev 2)
II.B.4.8. Annex to the PSMF

Finding PSMF

The marketing status of [redacted] in the UK was incorrectly presented in the PSMF as not-marketed; however, sales figures show the product has been marketed in the UK for at least the last 3 years.

[redacted] is authorised in the EU under exceptional circumstances, subject to additional monitoring and additional risk minimisation measures that must be implemented in the UK. This finding has been graded as major as the breach of the requirements in GVP Module II directly impacts the ability of the MHRA's GPvP inspectorate to appropriately assess the pharmacovigilance system against the PSMF in accordance with article 111(8) of Directive 2001/83/EC (as amended).

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

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[redacted]

Preventative Action(s)
[redacted]

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

C.4.3 Minor findings

MI.1 Data management

During this inspection, several outputs from the safety database were reviewed in detail to assess the effectiveness of data cleaning activities completed in November 2019. Some data inaccuracies were identified which were reviewed by Ipsen during the inspection. Ipsen have confirmed that the inaccuracies have no impact on routine regulatory submissions. However, it should be noted that there may be unexpected consequences of these errors on ad hoc reports, and the ability for Ipsen as MAH to ensure that collected reports are accurate, consistent, verifiable and as complete as possible for any clinical assessment conducted on stored data in the future, in accordance with GVP Module VI.B.1.

Finding MI.1 a)
Three cases classified as non-serious were identified to contain serious events despite mechanisms put in place by Ipsen to ensure that cases with serious events are always serious at case level. The affected cases were: • [redacted] • [redacted] • [redacted] The Data Monitoring Query (DMQ) established by Ipsen in November 2019 to check inconsistencies in seriousness at case level and event level did not identify the three cases.
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.1 b)

Permutations of the same study ID were assigned to different cases received from the same study due to errors in the ARISg study library.

For example:

- [redacted]

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[redacted]

Study ID consistency was addressed during the data cleaning activities in November 2019; however, for the above example, Ipsen confirmed that the extra space was not identified at the time of the mapping review.

Other examples identified included:

- SPECIAL DRUG INVESTIGATION
  SPECIAL DRUG USE INVESTIGATION
- [redacted]

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]	

Finding MI.1 c)

In the safety database, the coding of each suspect product included the following fields:

- Product Name as Reported
- Product Description
- Preferred Product Description

Examples were identified where the "Product Name as Reported" was incorrect based on the reported suspect product:

- Case [redacted] was reported for two suspect products, [redacted] The case contained two suspect product records, one correctly populated for [redacted]', and the second with a Product Name as Reported incorrectly populated with [redacted] instead of [redacted]

- Case [redacted] was reported for two suspect products [redacted]. The case contained two suspect product records, one correctly populated for [redacted] and the second with an incorrect PNR of [redacted] instead of [redacted]

Ipsen committed to correcting these cases and conducting a specific data review in the entire database to identify similar data entry errors and correct the corresponding cases.

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[redacted]

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[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]

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.

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA pharmacovigilance inspection to review the remediation of the 2018 critical finding for the quality management system is conducted in the next 12 months.

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.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Ipsen	**DATES**	w/c 27 April - May 2020

Inspection plan

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This inspection will be product-specific and will focus on data clean-up activities and the [redacted] submitted in November 2019.

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

Formal interview sessions with company personnel will not be conducted, however, we request that you provide a designated contact point who can assist with any ad hoc questions from inspectors or arrange calls between inspectors and SMEs as required.

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

Ipsen designated contact point:

[redacted]

BACK-UP:

[redacted]

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Opening meeting: w/c 27 April 2020

There will be an opening meeting to review the scope of the inspection. Ipsen are asked to lead a company presentation which aims to orientate the inspectors around the CAPA implemented in relation to the safety database and all data cleaning activities. This presentation should last no longer than 20 minutes.

[redacted]

Topics

- Consistency and accuracy of data in the safety database and robustness of data extraction from the safety database
- [redacted] case data inclusion

Closing meeting: date tbc

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