Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Takeda

MHRA Inspection Number: Insp GPvP 16189/10920657-0003

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

Table of Contents

ABBREVIATIONS

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

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

SECTION A: INSPECTION REPORT SUMMARY

Section 40 and 43

Inspection type:	Statutory National Inspection
System(s) inspected:	Takeda [redacted]
Site(s) of inspection:	61 Aldwych, Holborn, London WC2B 4AE
Main site contact:	[redacted]
Date(s) of inspection:	18 – 21 June 2019
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	15 – 18 November 2016 16 – 19 June 2015 16 – 18 April 2012 19 – 22 October 2009 25 – 28 January 2005
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 the [redacted] products were selected.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Argus Safety V8.1.2 (commercially available)
Key service provider(s):	• Case processing services outsourced to Cognizant. • For the established products portfolio (called Established products, Inspired Collaboration "EPIC"), activities including regulatory affairs, case processing and PSUR production had been outsourced in an agreement with IQVIA. • Takeda had an agreement with PRA Health Sciences as the preferred strategic partner to manage operational activities across the R&D organisation.
Inspection finding summary:	5 Major findings 2 Minor findings
Date of first issue of report to MAH:	27 August 2019
Deadline for submission of responses by MAH:	07 October 2019 (1) 18 November 2019 (2)
Date(s) of receipt of responses from MAH:	07 October 2019 14 November 2019 (2)
Date of final version of report:	25 November 2019

Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Takeda 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 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.

Takeda is a research and development focused global pharmaceutical company with headquarters in Osaka, Japan, and operations in more than 130 countries. Pharmacovigilance activities are overseen by the Global Patient Safety Evaluation (GPSE) organisation, which is positioned within Takeda Global Research and Development (R&D). The GPSE organisation resides over four regional hubs, Osaka, Japan; London, UK; Massachusetts, USA; and Illinois, USA. Additionally, there are a limited number of GPSE personnel located at an office in Singapore. Local pharmacovigilance is conducted by local operating companies (LOCs). Takeda has approximately 70 LOCs worldwide, which report into the Takeda commercial organisation.

Takeda has a strategic partnership with PRA Health Sciences and has outsourced routine maintenance activities (including regulatory affairs, case processing and PSUR production) for their established products portfolio (EPIC) to IQVIA.

The inspection was conducted at a time when Takeda had announced the acquisition of Shire. A draft integration plan was reviewed by the lead inspector prior to the inspection. At the time of the inspection the Takeda and Legacy-Shire pharmacovigilance systems were operating as separate systems. The anticipated completion date in the draft integration plan was the end of the 2019 financial year, prior to moving into a monitoring period to assess the integration model.

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at Takeda's offices in London. Takeda personnel were available both on-site and via teleconference through 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 III).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (V24.1 dated 26th February 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

In general, the inspection was performed in accordance with the Inspection Plan. There were two additional days of office-based inspection conducted following the on-site days to complete the review of documentation.

The inspection was not completed during the onsite days and an interim closing meeting was held on 21st June 2019 at the Takeda offices, to summarise the inspection status and to provide preliminary feedback regarding the inspection findings. The inspection was concluded via office-based document review and a formal closing meeting was conducted via teleconference on 10th July 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 2016 the company had made the following changes to the pharmacovigilance system:

Section 43

- On the 8th January 2019, Takeda completed the acquisition of Shire. At the time of the inspection, integration activities had only just begun. The Shire pharmacovigilance system [redacted] remained separate from the Takeda system [redacted]
- The EUQPPV had changed from [redacted] to [redacted] in January 2019. Following the completion of the Shire acquisition, The EUQPPV changed again, to [redacted] the EUQPPV of the legacy Shire system, in March 2019.
- Following the change of EUQPPV to [redacted] the location of the PSMF was moved from the Takeda office in London to the legacy Shire office in Sweden. This move changed the Supervisory Authority for Takeda from the MHRA to the Swedish Medicinal Products Agency (MPA).
- In February 2017, Takeda acquired ARIAD Pharmaceuticals Inc. This brought two oncology products, Iclusig [redacted] and [redacted] into Takeda's portfolio.
- In June 2018, Takeda acquired TiGenix, which brought the product [redacted] into Takeda's portfolio. [redacted] was authorised in the EU through the centralised procedure on 23rd March 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 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 Post-Authorisation Safety Studies

Requirements:

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

VIII.B.4.3.2 *"The final study report should include the following information:*
10.6 Adverse events and adverse reactions: summary of all adverse events/adverse reactions collected in the study, in line with requirements described in GVP Module VI."

GVP Module VI – Management and reporting of adverse reactions to medicinal products (Rev 2)

VI.A.1.6 *"Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered serious."*

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 and shall ensure that the confidentiality of the records of the study subjects remains protected [IR Art 36]. This provision should be also followed for PASS required in the risk management plan agreed in the EU or conducted voluntarily in the EU.*

For ease of reference, the sub-parts to this finding are related to two separate PASS, and the procedural documentation governing the management of PASS:

Section 43

- Findings MA.1 a) – d) are related to the [redacted] conditional PASS (MA25101);
  - The EU marketing authorisation for [redacted] was conditional pursuant to Article 14(7) of Regulation (EC) [redacted] and Takeda was required to complete a PASS: Study MA25101, An Observational Cohort Study of the Safety of [redacted] in the Treatment of Relapsed or Refractory [redacted] Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma.
- Finding MA.1 e) relates to the [redacted]
  - The EU RMP [redacted] dated 05-July-2018, approved; and [redacted], dated 01-Feb-2019, submitted for approval) outlined a Category 3 PASS: Study [redacted] An

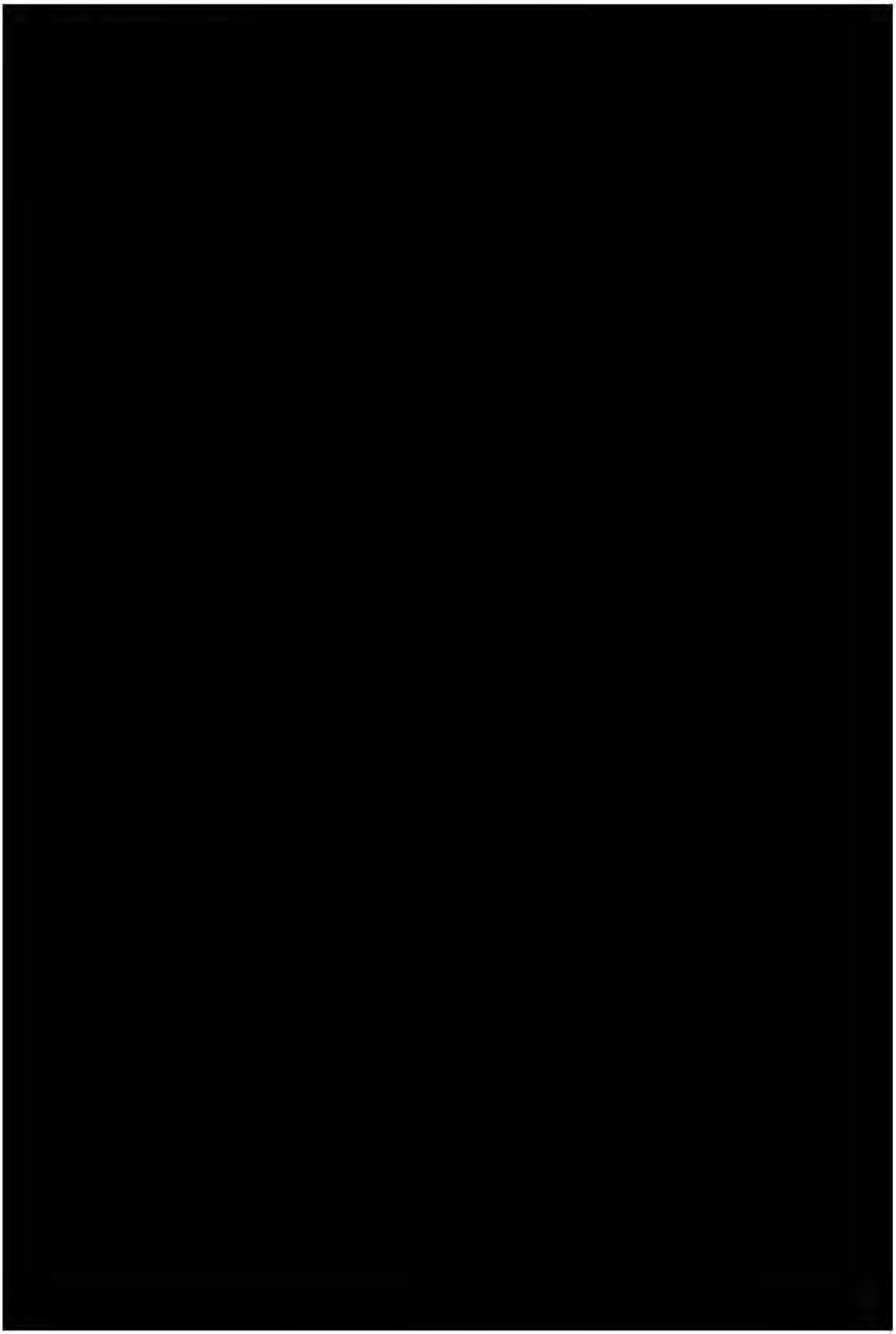
Section 43

international observational prospective cohort study comparing [redacted] to other biologic agents in patients with ulcerative colitis or Crohn's disease.

- Finding MA.1 f) relates to the procedural documentation supporting the management of PASS.

Finding MA.1 a)
There were discrepancies identified between the study database and the global safety database for adverse event reports from the [redacted] conditional PASS. Takeda confirmed that the end of data collection occurred in October 2018 and the clinical database was locked in November 2018. A final SAE reconciliation was performed on 08-Nov-2018. During the inspection, examples were identified of events that had been upgraded to serious in the global safety database following receipt of follow-up information from the sites which showed the investigator assessed the event as serious (medically significant); however, this follow-up was not captured in the clinical database. The examples included: • For case [redacted] the event of neuropathy peripheral is appropriately captured in the safety database as serious based on a follow up received from the site on 13-Apr-2018, which showed the investigator assessed the event as serious (medically significant). This follow up was not captured in the clinical database. • For case [redacted] the event of neuropathy peripheral is appropriately captured in the safety database as serious based on a follow up received from the site on 03-Apr-2018, which showed the investigator assessed the event as serious (medically significant). This follow up was not captured in the clinical database. • For case [redacted] the event of neuropathy sensory peripheral is appropriately captured in the safety database as serious based on a follow up received from the site on 03-Apr-2018, which showed the investigator assessed the event as serious (medically significant). This follow up was not captured in the clinical database. The [redacted] EU RMP lists peripheral neuropathy (sensory and motor) as an important identified risk. Takeda confirmed that the final study report is currently under preparation. It should be emphasised that only a small number of PTs were reviewed for this study during the inspection and Takeda should investigate the extent of the issue and the root cause of why this was not identified during the SAE reconciliation activity.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

Section 43



Section 43

[redacted]

Section 43

[redacted]

Corrective Action(s)
[redacted]

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

Section 43

Preventative Action(s)	
[redacted]	
[redacted]	

Finding MA.1 b)

The Data Management Plan (DMP) [redacted] dated 26-Mar-2018) for the [redacted] conditional PASS included a listing of manual data checks that would be performed for this study in Appendix A. Section 11.2 (Manual Data Review) of the DMP stated *"All data, both Complete and Incomplete, will be subject to manual review in accordance with the pre-specified checks defined in Appendix A."*

Examples were identified of manual data checks in Appendix A for which no evidence could be provided to demonstrate that these had been performed during the most recent review activity (conducted in September and October 2018). These included the following Manual Review Check IDs:

- [redacted]
- [redacted]
- [redacted]

A selection of these are detailed below to demonstrate the nature of these checks.

Manual Review Check ID	CRF Item	Check (in plain English)	Frequency
[redacted]			

Section 43

[redacted]

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]	[redacted]

Finding MA.1 c)

The Adverse Event Reconciliation Plan [redacted] dated 01-June-2017) for the [redacted] conditional PASS, Section 10 (Data items to be reconciled) stated that the subject number must match exactly between the safety database and the clinical database. There were seven cases in the safety database for which the subject ID had not been entered in the correct format of <Site ID> - <Subject ID> (or the historic convention of <Subject ID>). Instead they had been entered as single digits or left blank. These discrepancies did not appear in the final SAE reconciliation report dated 08-Nov-2018.

Case number (MCN)	Subject ID in safety database	Subject ID
[redacted]		

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

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

Finding MA.1 d)
The Monitoring Plan [redacted] dated 11-June-2018) for the [redacted] conditional PASS, Section 8.6 (Site Management Calls) stated: *"Once a site is initiated all remote activities will be performed by the SM* [Site Manager] *in collaboration with the CRA* [Clinical Research Associate]. *During the first year SM will conduct biweekly calls, and thereafter monthly calls will be done using the Script/Guidance for Follow-up calls discussion.* […] *For sites with no more active patients in the study, it is not required to have monthly calls with the sites."* For UK site [redacted] the most recent site management call was held on 18-July-2017 even though the last patient last visit was 11-Sep-2018 and the site close out visit date was 19-Feb-2019.
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

[redacted]	

Finding MA.1 e)

The following finding was identified in relation to [redacted] PASS study [redacted]

The Safety Management Plan [redacted] dated 28-Jan-2019) Section 4.4 (Safety database reconciliation) stated:

"Reconciliation of serious adverse events (subjects with vedolizumab exposure only) between the clinical database and Takeda Global Safety Database will be conducted on a monthly basis by Mapi Safety. Reconciliation will be performed monthly until the study is complete by comparing a listing of SAEs from the clinical database, which is maintained by Mapi, with a listing of SAEs from the Takeda Global Safety Database."

Takeda was asked for the rationale for why non-serious adverse events were not being reconciled, as they were also being collected and recorded in the study and sent to Takeda Drug Safety for inclusion in the global safety database.

Takeda stated *"Other than SAEs, non-serious Adverse Events of Special Interest (AESIs) are being reconciled for study [redacted] These non-serious AESIs do appear in the reconciliation reports along with the SAEs."* However, there was no evidence of non-serious adverse events in any of the reconciliation reports provided to inspectors.

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]	

MHRA request for further clarification

[redacted]

Takeda clarification response

[redacted]

Section 43

[redacted]

Finding MA.1 f)

The written procedures describing the management of non-interventional studies [redacted] "Non-interventional Studies", [redacted] effective 12-Jan-2019 and [redacted] "Protocol Development, Review and Approval for Post Approval Safety Studies (PASS) and Post-Marketing Surveillance (PMS) Studies", [redacted] effective 12-Jan-2019) did not adequately describe the processes to comply with specific EU regulatory requirements for non-interventional post-authorisation safety studies. For example:

a) Submission of study protocols and protocol amendments for imposed studies to the Pharmacovigilance Risk Assessment Committee (PRAC) for review and approval.

b) Submission of final study results to the PRAC (for imposed studies) or to the competent authorities of the Member States in which the study was conducted (for voluntary studies) within 12 months of the end of data collection.

c) In addition [redacted] section 3.9.4. stated *"If required by national law or regulation, the Investigator shall report serious adverse drug reactions suspected of being related to the studied Takeda product to the applicable regulatory authorities and IRB/EC within the timelines required by such law or regulation."* It was confirmed that Takeda as the sponsor was responsible for reporting ADRs to EU regulatory agencies and both serious and non-serious ADRs from Takeda Sponsored NIS are reported to EU regulatory agencies.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

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

MA.2 Pharmacovigilance for Biological Medicines

Requirements:

GVP Product- or population- specific considerations II: Biological medicinal products

P.II.B.4. *"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 […]*

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) […]

Any signal should be evaluated in the context of batch-specific exposure data, including numbers/codes of delivered or sold batches, their size and the regions or countries where the respective batches have been delivered."

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

Section 43

Takeda held marketing authorisations for the biological medicines [redacted] and [redacted] and were therefore subject to the considerations outlined in GVP Product- or population- specific considerations II: Biological medicinal products (GVP P.II).

Finding MA.2 a)

Takeda had failed to meet the requirements for MAHs of biological medicines for signal management activities.

The evidence of signal detection activities that was reviewed during the inspection for [redacted] for period October – December 2018) and [redacted] for July 2018 and April 2019) did not include any mechanism to support the detection of any apparent changes in suspected adverse reaction reporting rates or trends between batches of the same product, such as batch trending or the analysis of denominator data (i.e. exposure information) alongside reports of suspected adverse reactions.

Furthermore, the procedural documents [redacted] effective 11-Nov-2018) and [redacted] effective 03-Apr-2019), which governed the signal management process at Takeda, did not reflect the specific requirements regarding signal management in relation to biologicals as stated in GVP PII.

It is acknowledged that adverse events associated with product quality complaints were routinely reviewed during signal detection activities and that any identified trends were further evaluated to determine any specific batch issues; however this would not detect emerging issues between batches of the same product, as is required in GVP P.II.

Section 43

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

Preventative Action(s)

[redacted]

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

Finding MA.2 b)

The EU SmPC and PIL for [redacted] on the EMA product page (date of last update 01-April-2019), and the UK-approved version uploaded to the EMC (SmPC dated 20-Feb-2019, PIL dated Feb-2019) did not include a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file in line with the requirements of GVP PII.

It was also noted that while the SmPC included the relevant wording, the EU PIL (date of last update 13-March-2019) and UK PIL (dated Feb-2019) for [redacted] did not include similar wording.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

MA.3 Risk Management

Requirements:

Commission Implementing Regulation (EU) No 520/2012 Article 34(3) *"The periodic safety update report shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment."*

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)

XVI.B.4. *"Evaluating the effectiveness of additional risk minimisation measures is necessary to establish whether an intervention has been effective or not, and if not why not and which corrective actions are necessary. The evaluation should be performed for the additional risk minimisation tools individually and for the risk minimisation programme as a whole."*

Section 43

Finding MA.3 a)

There were deficiencies identified with the measurement of the effectiveness of risk minimisation in place for [redacted]

The EU RMP [redacted] dated 05-July-2018, approved; and [redacted] dated 01-Feb-2019, submitted for approval) included the important potential risks of infections, including gastrointestinal infections and progressive multifocal leukoencephalopathy (PML). Takeda had introduced additional risk minimisation measures (aRMMs) to inform healthcare professionals and patients of the potential risk of serious infections including opportunistic infections and PML, and the need to be vigilant of neurological signs and symptoms that may indicate early onset PML. These risk minimisation measures were first implemented in the UK in June 2014.

The EU RMP stated, in section [redacted] "Additional Risk Minimisation Measures" for both the patient alert card and the healthcare professional guide, that the effectiveness of risk minimisation measures would be measured by:

- *"Evaluation of the effectiveness of the proposed risk minimisation measures for opportunistic infections will be measured by the incidence, character, seriousness, and severity of reported opportunistic infections.*
- *Evaluation of the effectiveness of the proposed risk minimisation measure for ensuring that patients with treatment-emergent neurological signs and symptoms are detected rapidly and referred to a neurologist will be measured by the time lapse between onset of symptoms and neurological referral reported in any spontaneous reports."*

The EU RMP stated that the evaluation of effectiveness would be reported in the PSUR.

The [redacted] PSUR dated 03-Jan-2018 (covering the period 20-May-2017 to 19-Nov-2017) section 16.5 (Effectiveness of Risk Minimization) did not include any detailed evaluation of the effectiveness of risk minimisation activities. Instead the following statement was included: *"Evaluation of the effectiveness of these risk minimization measures will be measured by evaluation of outcomes from the PASS. Outcomes will also be indirectly evaluated through routine pharmacovigilance."*

While it is acknowledged that the important potential risk of opportunistic infections and PML

was discussed in PSUR section 16.3.1. (Information on Important Potential Risks), this discussion was not in the context of the effectiveness of risk minimisation and there was no reference to any analysis of the time lapse between onset of symptoms and neurological referral in spontaneous reports.

Section 43

When determining the CAPA for this finding, the company should consider whether the design of the PASS [redacted] is appropriate for evaluating the effectiveness of the [redacted] ncluding whether time-lapses from the onset of neurological symptoms to referral is information which is routinely collected in the study.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

Comment

Takeda had several scenarios in which targeted follow-up questionnaires were required per RMPs. It was noted that the wording in the recently updated procedural document did not provide sufficiently clear instructions on the sending of these, referring to some as 'product-specific optional' forms.

[redacted] "Targeted Follow-Up Job Aid" [redacted] effective 26-Apr-2019) Section three, outlined four different categories that these follow-up forms were divided into. The first were regulatory required form, the second were product-specific optional forms, the third were general (i.e. non product specific) which were optional, and the final category were routine case-processing forms, with an example given of pregnancy follow-up. Section four of the TOOL stated regulatory-required must be sent, and optional forms may be sent if requested by the physician conducting medical review of the case.

Appendix one outlined the forms which were regulatory requirements and those which were optional. The [redacted] dated 06-Mar-2017) was reviewed, Annex seven contained several required targeted follow-up questionnaires related to important identified, and important potential risks:

- Targeted Follow-up Questionnaire: Severe Hypersensitivity Skin Reactions (including necrotic skin lesions)
- Targeted Follow-up Questionnaire: Pancreatitis
- Targeted Follow-up Questionnaire: Hepatic events
- Targeted Follow-up Questionnaire: Malignancies (including pancreatic cancer)

All four of these forms were included in the "optional" list, resulting in them being sent only when a physician at medical review requested them.

Takeda may wish to consider the terms "regulatory required" and "optional" within this work instruction. The requirement for physicians to review the provided information and request required information via a targeted follow-up questionnaire is in line with GVP Module XI.B.3, to ensure that follow-up methods should be tailored towards optimising the collection of missing information. Takeda may also wish to consider a review of [redacted] "Medical Review of Safety Reports in or Generated from the Global Safety Database" [redacted] effective 03-Apr-2019) which stated:

"(e) For partner cases and LOC cases, standard and targeted follow-up queries will be performed by the case originators without being prompted by Medical Reviewers."

MA.4 Management and Reporting of Adverse Drug Reactions

Requirements:

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

VI.A.1.6. *"Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered serious"*

VI.B.5. *"marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR submission and case archiving"*

VI.B.1.2. *"With regard to the submission as ICSRs, solicited reports should be classified as study reports. They should have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria"*

VI.C.1.2. *"In line with ICH-E2D (see GVP Annex IV), these collected adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medicinal products."*

VI.B.8. *'With regard to the content and format of electronic ICSRs, competent authorities and marketing authorisation holders should adhere to the following internationally agreed ICH guidelines and standards (see GVP Annex IV) taking into count the transition from ICH-E2B(R2) to ICH-E2B(R3) formats:*
[…]
• the latest version of the Guide for MedDRA Users MedDRA Term Selection: Points to Consider15;'

MedDRA Term Selection: Points to Consider (Release 4.17 based on MedDRA Version 22.0)

2.3 *"Do Not Alter MedDRA MedDRA is a standardised terminology with a pre-defined term hierarchy that should not be altered. Users must not make ad hoc structural alterations to MedDRA, including changing the primary SOC allocation; doing so would compromise the integrity of this standard."*

Finding MA.4 a)

Cases in the global safety database which had been marked for deletion had not been deleted and remained available for inclusion within regulatory reports and signal detection activities. The cases reviewed during the inspection had been marked for deletion as they were duplicate cases.

There were almost 200 individual cases which had been marked for deletion, related to EU-authorised products, which contained a suspect drug and at least one event; the earliest receipt date was January 2016.

Section 43

Procedural document [redacted] "Handling of Individual Case Safety Reports (ICSRs) – Job Aid" [redacted] effective 20-Jan-2019) stated that designated users with deletion permissions are responsible for ensuring that cases with action items for "Case Deletion Request" are actioned. There were no timeframes associated with this activity, either from the identification that a case requires deletion to being deleted, or frequency defined for designated users to filter action items and delete cases.

Takeda confirmed that, although the cases had been marked for deletion, they would not have been excluded from any Cognos reports, resulting in their potential inclusion for signal detection and PSURs. Of note, there were 77 cases which had [redacted] as a suspect drug, which is on a six-monthly PSUR cycle.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

Finding MA.4 b)
The following deficiencies were identified with regards to causality assessments: a) Cases were identified where there was no reporter or company causality present in the global safety database. Cases [redacted] and [redacted] were both solicited cases which had been originally assessed by the reporter and company, as not-related. However, both cases had been updated to correct spelling errors which had left the causality fields blank in the database. Upon further review, the line listing provided to the inspection team which included all cases received from 01-Jan-2016, indicated there were ove[redacted]events from [redacted] cases (including [redacted] and [redacted] which had blank reporter and company causality fields. Takeda confirmed that all events which did not have reporter or company causality

entered into the case would default to "related" within the Cognos reports being utilised for signal detection and PSURs.

b) Spontaneous cases which had been assessed as not-related by reporter and company were being included within data outputs provided to PSUR authors. Takeda confirmed that the Cognos searches set-up for retrieving data for PSURs from the global safety database did not exclude events which were deemed to be unrelated to the suspect medicine.

Takeda are reminded of the requirements outlined in VII.B.5.6.3. regarding the inclusion of adverse drug reactions in the cumulative and interval summary tabulations for post-marketing data sources and should comment on the impact of the above on aggregate reports within the responses to this finding.

Section 43

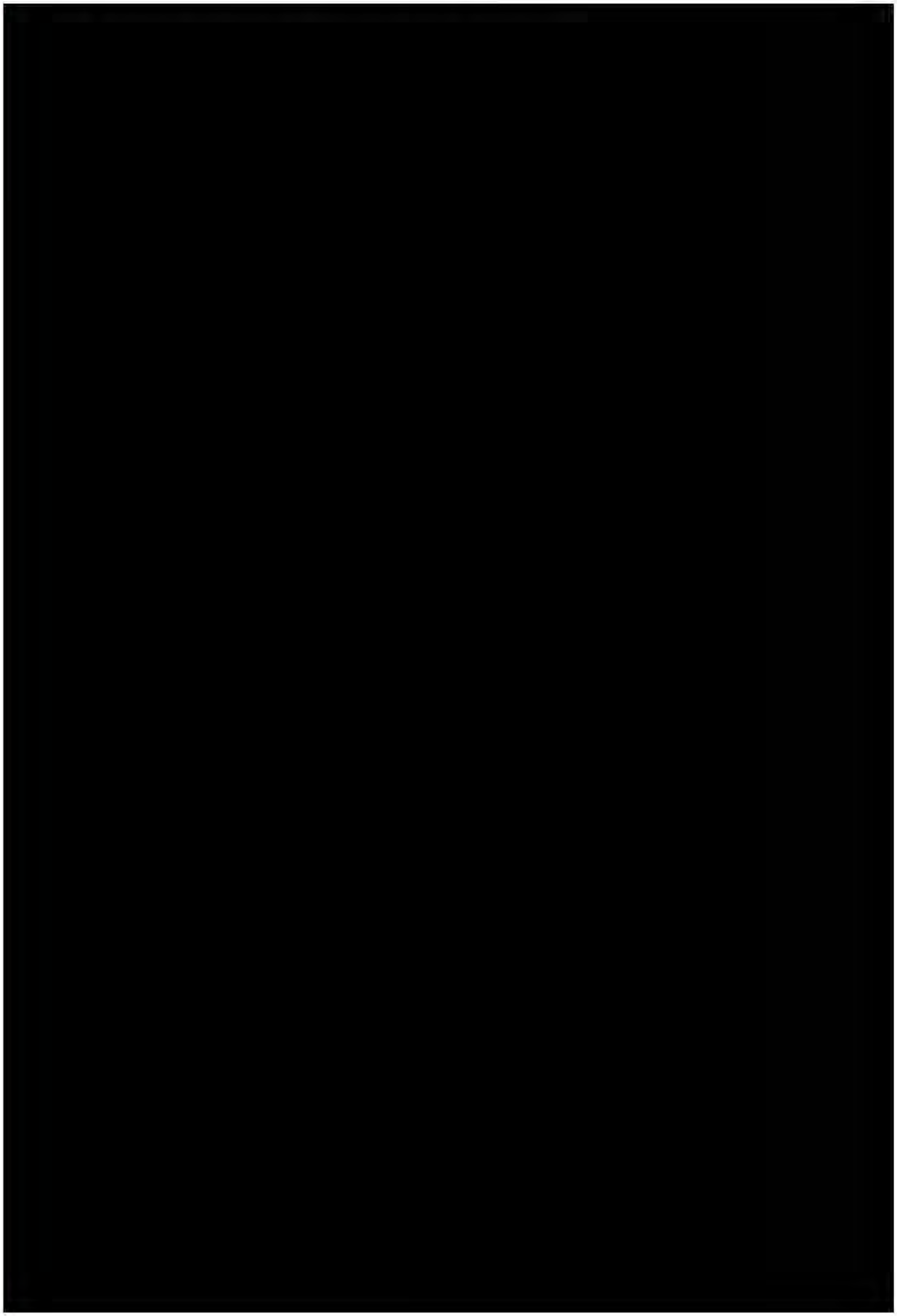
Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43



Section 43

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

Preventative Action(s)
[redacted]

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

Section 43

[redacted]

Finding MA.4 c)
There were examples where events had been coded to non-primary System Organ Class (SOC) in MedDRA: • The PT "gait disturbance" had been coded to the musculoskeletal and connective tissue disorders SOC in case [redacted] The primary SOC for "gait disturbance" is general disorders and administration site conditions. • The PT "Injection site abscess" had been coded to the general disorders and administration site conditions SOC in cases [redacted] and [redacted] The primary SOC for "Injection site abscess" is the infections and infestations SOC. There is the potential for non-primary SOC selection to impact upon signal detection and the presentation of safety data within aggregate reports.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

Section 43

[redacted]

Corrective Action(s)
[redacted]

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

Section 43

[redacted]

Preventative Action(s)
[redacted]

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

Comment
There were delays identified with closing action items being used for follow-up. Procedural document [redacted] "Handling of Safety Information" [redacted] effective 26-Apr-2019) appendix 3 "Follow-up" outlined Takeda's approach for follow-up activities. Timeframes were outlined for serious spontaneous and serious post-marketing solicited reports, that an initial follow-up should be sent within 10 days, and a second attempt should be made within 45 calendar days of the first follow-up attempt. There were no timeframes associated with other case-types, or a minimum or maximum amount of attempts described; though non-AE cases (such as special situation reports and pregnancy reports) were expected to have a single follow-up attempt be made for further information. Procedural document [redacted] "Medical Review of Safety Reports in or Generated from the Global Safety Database" [redacted] effective 03-Apr-2019) outlines that, if the medical reviewer asses that a query should be raised with the reporter, or their healthcare

professional, or additional follow-up is required, they are required to open an action item within Argus and specify the information that is required. The case will be routed to the LOCs, for the follow-up to be performed, and the action item updated with a completed date.

A review was conducted of the timeliness of the action items which had been opened by medical reviewers and over 7,000 action items had been completed after the due-date assigned. There were also six action items which had been open for over 90 days where no due-date had been assigned to it. Appendix II contains examples which were identified.

Whilst having action items remain open or closing action items after an assigned due-date is not a breach of legislation, Takeda are encouraged to review this process to ensure that tracking mechanisms for follow-up are robust. Although there were no examples identified where follow-up was not sent, Takeda are encouraged to review this in light of the information provided in this report.

MA.5 Quality Assurance

Requirements:

Directive 2001/83/EC as amended

Article 104 (2) *"The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented."*

Commission Implementing Regulation 520/2012

Article 13(2) *"Corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. A report on the results of the audit shall be drawn up for each audit and follow-up audit."*

Section 43

Finding MA.5 a)

There were examples identified where CAPA plans had not been agreed for audits conducted in 2017, and early 2019.

- Audit [redacted] (audit report date 28-July-2017) had one major finding listed in the PSMF concerning computerised systems. A CAPA plan had not been agreed at the time of the inspection and no evidence could be provided of any actions taken to address this issue.
- Audit [redacted] (audit report date 28-July-2017) had one major finding listed in the PSMF concerning AE reporting. A CAPA plan had not been agreed at the time of the inspection and no evidence could be provided of any actions taken to address this issue.
- Audit [redacted] (audit report date 06-Feb-2019) had two major findings listed in the PSMF concerning market research and patient support programmes. It is acknowledged that a meeting took place in March 2019 to discuss the responses but a CAPA plan had not been agreed at the time of the inspection.

Global Standard [redacted] "Managing GxP Related Events and CAPA" (V3.0, effective 30-Jan-2019), stated *"Takeda event investigations must be completed within the period defined by Takeda procedure(s), which may not be longer than 30 calendar days."* It was noted that the weekly report on the status of CAPAs, which was generated from the QAAD system (repository for GCP/GVP audits and quality events), did not include audits / quality events for which CAPAs had not been agreed yet.

Root Cause Analysis

[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

Section 43

[redacted]

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

C.4.3 Minor findings

MI.1 Quality Management System

Section 43

Finding MI.1 a)
There were deficiencies identified with the procedural documentation supporting ongoing safety evaluation: a) [redacted] "Global Safety Management" [redacted] effective 15-Nov-2018) stated that the Global Safety Lead (GSL) determines the frequency of SMT meetings and recommends they are held at least quarterly. Where a meeting is not deemed necessary there is a requirement for this decision to be documented. There were examples where SMTs had not been held which were not supported by the documentation, per PROC-[redacted] • The decision(s) not to hold an SMT for [redacted] since January 2018 was not supported by any documentation. • The decision to not hold an SMT meeting for [redacted] between June and December 2018 for [redacted] was not supported by any documentation. b) There was no procedure which outlined that all CCDS' with a common active-substances should be reviewed concurrently to ensure that the safety information was aligned across all CCDS' if one of the CCDS' was updated. The impact is considered to be minimal as examples were seen during the inspection where this process was done in practice.
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)	Due Date(s)
[redacted]	

Finding MI.1 b)

There were deficiencies identified with the training of key personnel who were responsible for distributing the [redacted] aRMMs.

The initial distribution plan was approved by MHRA on 28-May-2014 and it stated *"After the initial distribution by mail at the time of launch, further distribution of the materials will be via our Medical Science Liaisons at their face to face visits with prescribers."* At the time of the inspection evidence of documented training on the aRMMs could only be provided for one of the three Medical Science Liaisons (MSLs). For the remaining two MSLs there were limited records available to fully demonstrate that they had received the training.

In May 2016 the MHRA approved a revised distribution plan for [redacted] aRMMs which included provision of materials by Key Account Managers (KAM) during their visits with prescribers. At the time of the inspection there were 18 KAMs (one of which joined the company in June 2019 and is not included in the figures below). Evidence of documented training on the aRMMs could be provided for seven KAMs. For ten KAMs there were limited records available to fully demonstrate that they had received the training.

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]	

MI.2 Provision of Information for Inspectors

Finding MI.2 a)
Discrepancies between case coding and the line listing provided to inspectors were identified: A selection of non-serious cases were selected from the line listing, however on review of the case files by the inspection team, the CIOMS forms showed the cases had been assessed as "Medically significant" and were serious. The case numbers included: [redacted] and [redacted] Takeda stated that the cases had been identified as serious cases in the safety database by including a statement of "SERIOUSOTHER" in the notes field on the case summary tab. **In the responses to this finding, Takeda should:** • **Comment on how these cases would be identified as serious cases within the Cognos searches used for regulatory reporting and assess any impact of this.** • **Comment as to how these cases were displayed as non-serious in the line listings given to the inspection team.** • **Comment on the impact to expedited reporting.**
Root Cause Analysis
[redacted]

Section 43

Section 43

[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]	

C.4.4 Comments

a) Takeda are reminded of the MHRA's expectation that the timeline between the decision to update the RSI and submission of the relevant safety variation should not exceed 6 months.
Takeda's procedures theoretically allowed a 9-month timeline from the date the decision is made to update the RSI to variation submission for low priority signals for which the submission class 3 'Other safety changes' is selected. In this scenario CCDS approval should occur with 3 months of the date the decision is made to update the RSI and the safety variation submission should be made within 6 months of CCDS approval. During

the inspection, Takeda stated that in practice no confirmed signal would be assigned to the class 3 variation submission category.

There were no examples were seen during the inspection of a time lag of more than 6 months between Day 0 and variation submission.

Section 43

b) Records of training on the [redacted] and [redacted] risk minimisation programme were reviewed for staff responsible for distribution.

- One Medical Information Officer received training on 19-June-2019 on the aRMMs for Instanyl (during the inspection). It is acknowledged that the other members of the UK Medical information team had received training on the Instanyl risk management programme in previous years.
- It was noted that one Medical Information Manager received training on 19-June-2019 on the aRMMs for [redacted] (during the inspection).
- The combined [redacted] training record for an MI Officer did not include a trainer signature or date. The header of the record indicated the training took place on 25-Apr-2019.

  The remaining members of the UK MI team received timely training on 09-Jan-2019 [redacted] aunched in the UK on 19-Feb-2019).

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.

Takeda should keep the MHRA informed of any changes to the timeframes, or activities associated with the Shire acquisition and subsequent merging of pharmacovigilance systems.

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).
- Directives 2001/20/EC and 2005/28/EC in relation to Clinical Trials.
- 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.
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".
- CHMP/ICH/309348/2008: E2F "Development safety update reports".
- EMA/CHMP/ICH/135/1995: E6 (R2) "Guideline for good clinical practice".
- Eudralex Volume 10, Chapter II: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT3'), June 2011.
- MedDRA Term Selection: Points to Consider.

APPENDIX II DELAYED ACTION ITEMS

Report Type	Case Number	Action Type	Action Description	Date Action Opened	Date Action Due	Date Action Completed	Days Action Open	Days after due date action completed
[redacted]								

Section 43

Table 1: Examples of Action Items with completion date exceeding due date

Section 43

Report Type	Case Number	Action Type	Action Description	Date Action Opened	Date Action Due	Date Action Completed	Days Action Open
[redacted]							

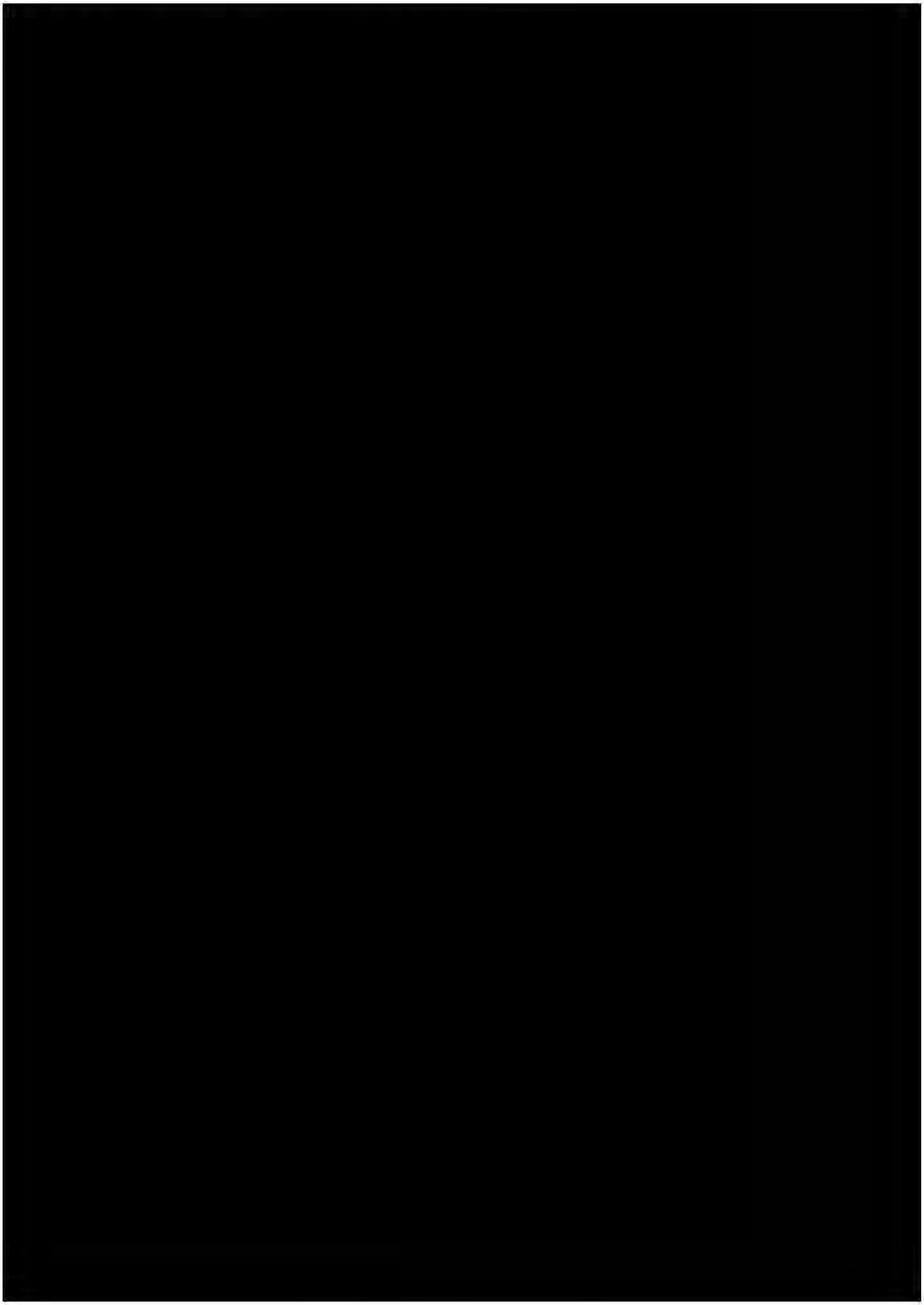
Table 2: Examples of Action Items with no completion date

APPENDIX III MA.4 B) UNRELATED SOLICITIED EVENTS

Case Number (MCN)	Case Report Type	Seriousness	Country	Suspect Drug (Generic Name)	Event (Serious and non-serious; MedDRA PT)
[redacted]					

Section 43

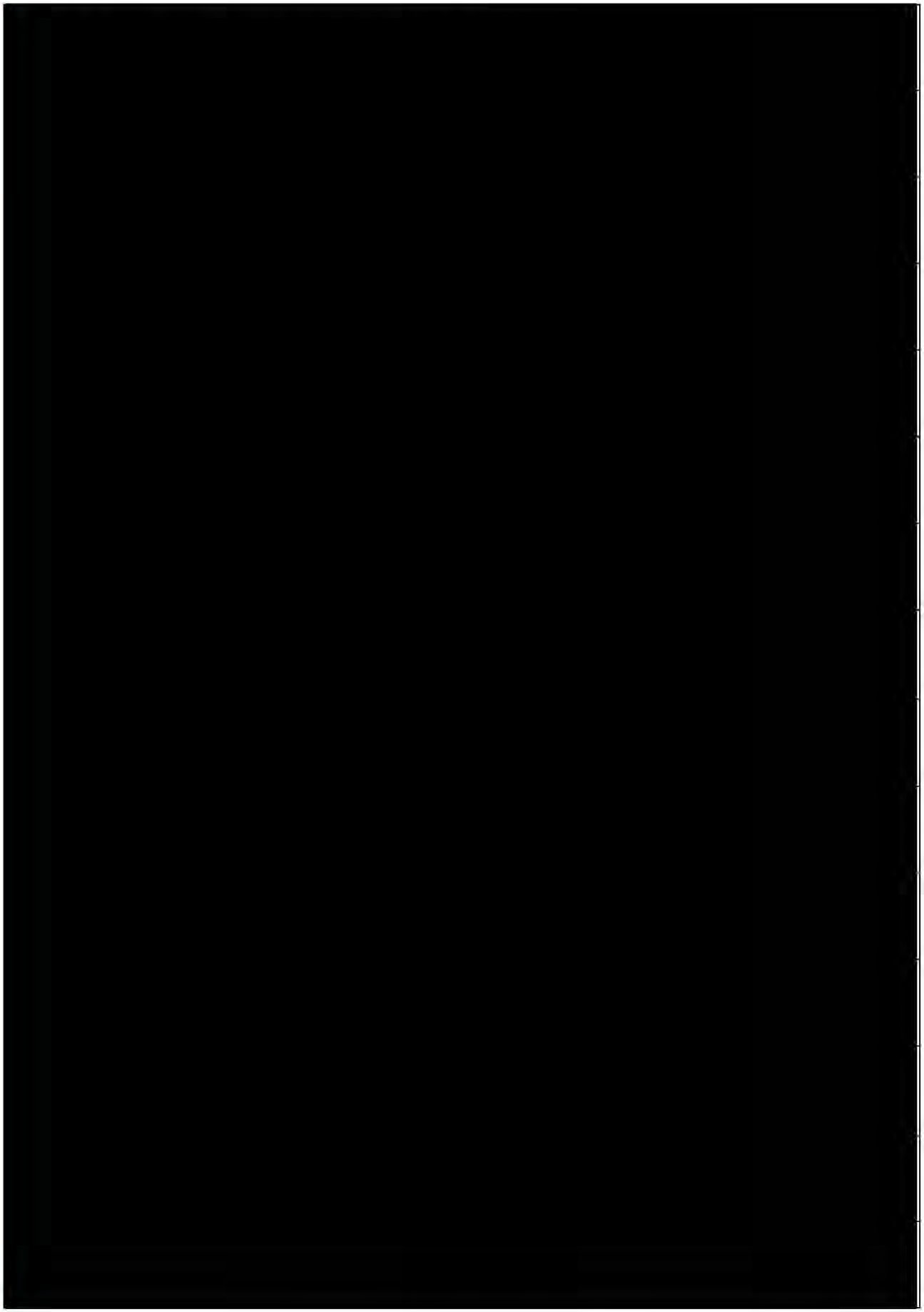
Section 43



Section 43

[redacted]

Section 43



Section 43

APPENDIX IV PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insert inspection number	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Takeda	**DATE**	18th June 2019
LOCATION	61 Aldwych, Holborn, London WC2B 4AE	**START TIME**	09:00 arrival for 09:30 opening meeting

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)*		[redacted]
LUNCH	-	-
ICSR processing, including but not limited to: - Data entry, - Case assessments - QC - Reporting - Follow-up processes	[redacted]	[redacted]
[redacted]		

Section 40

MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Takeda	**DATE**	19th June 2019
LOCATION	61 Aldwych, Holborn, London WC2B 4AE	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Risk Management, including but not limited to: - Implementation of additional risk management activities - Studies as required in risk management plans	[redacted]	[redacted]
LUNCH	-	-
Signal Management, including but not limited to: - Signal detection, including monitoring of Eudravigilance data - Signal assessment/evaluation	[redacted]	[redacted]

Section 40

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Takeda	**DATE**	20th June 2019
LOCATION	61 Aldwych, Holborn, London WC2B 4AE	**START TIME**	09:00

Section 40

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Reference Safety Information, including but not limited to: - Safety variation submission - Post-approval implementation	[redacted]	[redacted]
LUNCH	-	-
Quality Management Systems, including but not limited to: - CAPA and deviation management	[redacted]	[redacted]
Periodic Safety Update Reports	[redacted]	[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Takeda	**DATE**	21st June 2019
LOCATION	61 Aldwych, Holborn, London WC2B 4AE	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
This day is reserved for document review and ad-hoc interview sessions as required.		Interviewees as required.
Closing meeting	-	All welcome