PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name:	Roche Products Limited
MHRA Inspection Number:	Insp GPvP 31/86087-0020

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AML	Additional Monitoring List
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CPD	Company Product Dictionary
CUP	Compassionate Use Programme
DRL	Drug Reference Library
DSR	Drug Safety Report
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorisation
FDA	U.S. Food and Drug Administration
GQ	Guided Questionnaire
GSDB	Global Safety Database
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
LLT	Lowest Level Term
LSU	Local Safety Unit
MAH	Marketing Authorisation Holder
MAP	Market Access Programme
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PBRER	Periodic Benefit Risk Evaluation Report
PDS	Product Development Safety Risk Management
[redacted]	[redacted]
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements

QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SDEA	Safety Data Exchange Agreement
SOP	Standard Operating Procedure
TCS	Tata Consultancy Services
TFUQ	Targeted Follow-up Questionnaire
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection
System(s) inspected:	Roche Products Limited [redacted]
Site(s) of inspection:	Day 1: Remote Days 2 – 4: Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW, UK
Main site contact:	[redacted] [redacted] Head QA Process, Product Development Quality (PDQ) F.Hoffmann- La Roche Ltd., Building 686, 4051 Basel, Switzerland Phone: [redacted] Email: [redacted]
Date(s) of inspection:	13 – 16 June 2022
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted]

Previous inspection date(s):	• GPvP 31/86087-0015: EU SA Inspection: 14 – 18 May 2018
	• PHV/2013/009: EU product-specific pharmacovigilance inspection for [redacted] and [redacted]
	  ● Inspection site one: 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK
	  29 – 31 October 2013 and 14 November 2013
	  ● Inspection site two: Genentech Inc. 1 DNA Way, South San Francisco, California, 94080, US
	  18 – 22 November 2013
	• GPvP 14878/86087-0007: MHRA national pharmacovigilance systems inspection: 16 – 20 January 2012 and 28 February – 01 March 2012
	• GPvP 31/86087-0005, EMEA/INS/PhV/2009/02: EU product-specific pharmacovigilance inspection for [redacted] 03 – 06 August 2009
	• GPvP 31/86087-002: MHRA national pharmacovigilance systems inspection: 19 – 22 February 2007 and 11 June 2007
	● 00031/0404: MHRA national pharmacovigilance systems inspection: 19 – 23 April 2004

Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	As part of the general systems review, specific signal detection processes and PSURs were examined for [redacted] and [redacted]
Name and location of UK QPPV:	[redacted] Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW, UK Phone: [redacted] Email: [redacted]

Global PV database (in use at the time of the inspection):	[redacted] (commercially available)
Key service provider(s):	• Tata Consultancy Services Ltd (TCS): Case processing services for all products. • Parexel International Ltd: Support for signal management, ICSR processes and medical writing.
Inspection finding summary:	0 Critical findings 1 Major finding 6 Minor findings
Date of first issue of report to MAH:	26 August 2022
Deadline for submission of responses by MAH:	30 September 2022 18 November 2022 06 March 2023
Date(s) of receipt of responses from MAH:	30 September 2022 15 November 2022 03 March 2023
Date of final version of report:	09 March 2023
Report author:	[redacted] Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Roche Products Limited (hereafter Roche) 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 UK and EU pharmacovigilance regulations and guidelines. In particular, reference was made to The Human Medicines Regulations 2012 as amended, Regulation (EC) No 726/2004 as amended, Commission Implementing Regulation (EU) No 520/2012 and the EU good pharmacovigilance practices (GVP) Modules as modified by the guidance note 'Exceptions and modifications to the EU GVP that apply to UK MAHs and the licensing authority'.

A list of reference texts is provided at Appendix I.

Roche is a global pharmaceutical company with headquarters based in Basel, Switzerland and offices across the globe. The Roche Group has two divisions: Pharmaceuticals and Diagnostics. The Roche pharmacovigilance (PV) system sits within the Pharmaceuticals division. The majority of global PV activities are centralised within Product Development Safety Risk Management (PDS) functions. Global PV functions are carried out across six main sites: Basel, Beijing, Shanghai, South San Francisco, Grenzach-Wyhlen and Welwyn in the UK.

The pharmaceutical product portfolio covers a number of therapeutic areas: oncology, immunology, infection diseases, ophthalmology and diseases of the central nervous system. At the time of the inspection, 11 UK authorised products were on the MHRA additional monitoring list (AML), including [redacted]
Particular focus was made on the inspection to review management of [redacted] ICSRs, signals and PSURs alongside those other products on the AML list.

Roche have outsourced several key PV activities to service providers and those pertinent to this inspection were:

- TCS – based in India, TCS conduct ICSR processing in the global safety database (GSDB), support for local safety units (LSU) ICSR intake, PVA maintenance support and market access programmes (MAP) management.
- Parexel – also based in India, Parexel conduct signal management and detection activities and support aspects of ICSR compliance.

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems. Day 1 of the inspection was conducted remotely with subsequent days (2-4) being on site at the offices in Welwyn. Personnel from PDS and other functions attended the site in order to participate in the inspection.

The inspection was performed using interviews and document review (including outputs from the GSDB 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).

Risk management topics were not reviewed and it is recommended that these areas are subject to review during a subsequent pharmacovigilance inspection.

B.3 Documents submitted prior to the inspection

The company submitted a UK PSMF [redacted] effective date 12 April 2022) 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 which is included in document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan and additional ad hoc discussions were held as listed in Appendix III.

The inspection was not completed during the scheduled days and an interim closing meeting was held on 16 June 2022 at the Welwyn office at 5pm. The inspection concluded with an additional 3 days of document review and no further closing meeting was deemed necessary following review completion.

A list of the personnel who attended the closing meeting is contained in the Interim 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, the company had made the following changes to the PV system:

- The role of the UK QPPV was fulfilled by [redacted] The EU QPPV remained as [redacted]
- The GSDB, [redacted], was upgraded from version [redacted] to [redacted] n April 2019. In February 2020, [redacted] was also upgraded to the E2B R3 standard.
- The new signal management system, [redacted] was introduced in March 2021.

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 that covers products authorised in respect of Northern Ireland which are graded as critical or major will be shared with the EMA, EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

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

C.4.2 Major findings

MA.1 Management and reporting of ADRs

Requirements:

Regulation (EC) No. 726/2004 as amended, Article 28(1)

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulations 187-188, Schedule 12A Part 6

Commission Implementing Regulation (EU) No. 520/2012, Chapter V

GVP Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) (as modified by the Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority)
VI.A.1.1. Adverse reaction, causality
"For regulatory reporting purposes, as detailed in ICH-E2D (see GVP Annex IV), if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore 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."

VI.B.2. Validation of reports
"d. one or more suspected adverse reaction (see VI.A.1.1. for definition).
[…]
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. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and the valid ICSR should be submitted."

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. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy (see VI.B.6.1. for guidance on the management of pregnancy reports), cases notifying the death of a patient, […]

Similarly, for suspected adverse reactions related to biological medicinal products, the definite identification of the concerned products with regard to their manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the names of the products and their batch numbers."

VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding
"a. Pregnancy
Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data, or reports which have a normal outcome should not be submitted as ICSRs since there is no suspected adverse reaction (see VI.B.2. for ICSR validation)."

The line listing provided for the purposes of the inspection included all cases for [redacted] and [redacted] received since 01 January 2019 (a total of approximately 95,500 cases containing ~ 286,000 events). During the inspection case files were reviewed for just under 50 cases.

The following deficiencies were identified:

Finding MA.1 a)

A number of examples were identified where serious and non-serious ICSRs had not been reported to the MHRA despite meeting the minimum reporting criteria:

i. A number of cases were not submitted to the MHRA due to the product name being selected from the company's Drug Reference Library (DRL), rather than the Company Product Dictionary (CPD); the latter of which drove regulatory submissions.

a. Six serious [redacted] cases were not submitted to the MHRA:
- [redacted], a spontaneous, serious case received on 14 October 2021 from the US reporting anxiety, bacterial pneumonia, acute hypoxic failure, electrolyte imbalance, anaemia, pulmonary embolism and productive cough.
- [redacted], a spontaneous, serious case received on 26 October 2021 from Italy reporting acute respiratory failure and shivers.
- [redacted], a spontaneous, serious case received on 24 November 2021 from Israel reporting COVID-19.
- [redacted], a spontaneous, serious case received on 22 November 2021 from the US reporting hyponatraemia, hypovolaemia, acute kidney injury and syncope.
- [redacted], a spontaneous, serious case received from Canada on 19 May 2022 reporting chills, dizziness, dyspnoea, hyperhidrosis, lethargy, malaise, oxygen therapy, pallor, tachycardia and tachypnoea.
- [redacted], a spontaneous, serious case received from Canada on 19 May 2022 reporting COVID-19, dependence on oxygen therapy and dyspnoea.

As a result of the DRL being selected, cases [redacted] and [redacted] were also not included in the [redacted] PSUR #1 covering the period 19 July 2021 – 18 January 2022.

Once this was raised with the MAH on inspection, the MAH conducted an additional analysis on all cases received from 01 January 2019 to 14 June 2022. This identified a total of 25[redacted] cases (10 serious and 15 non-serious) and

22 [redacted] cases (6 serious and 16 non-serious) that had not been included in their respective PBRERs as the DRL entry for the product name had been selected rather than the CPD.

b. Two ICSRs for [redacted] were identified that had not been submitted to the MHRA:
- [redacted], a non-serious UK case received on 02 December 2021, with an ADR of welts.
- [redacted], a non-serious UK case received on 15 May 2021, with an ADR of pruritus.

During the inspection, the MAH conducted a review of all [redacted] cases (542 in total) which were included in the line listing provided for the purpose of inspection. This identified an additional five serious and seven non-serious cases where the product name had been selected from the DRL rather than the CPD.

As part of the responses to the inspection report the MAH should conduct a further assessment to identify the true impact of cases not reported to the MHRA and other competent authorities. Information on the number of cases affected should be included.

ii. Inappropriate causality assessments led to several [redacted] cases not being submitted to the MHRA.

a. Two spontaneous cases for [redacted] were not reported to the MHRA due to incorrect causality assessments entered into the database:
- [redacted] was a spontaneous case for [redacted] reported from Australia, received on 25 January 2022, reporting a serious reaction of 'neutrophil count decreased'.
- [redacted] was a spontaneous case for [redacted] reported from the UK, received on 21 October 2021, reporting the non-serious AE of a sore throat and the special situation of 'drug dose administration interval too long.

As the reporter causality was not present in either of the cases, during case processing this should have been selected as 'Unknown' or 'Not reported'. However, reporter causality for both cases was incorrectly entered as 'Not applicable'. As company causality was also entered as 'Not applicable' (due to spontaneous cases having implied causality, as described in the [redacted] this led to the reporting rules not being triggered.

b. Two literature cases arising from a study for [redacted] (company received date of 15 March 2022) that reported serious ADRs had not been submitted to MHRA due to incorrect coding of reporter causality.
- Case [redacted] reported placental insufficiency during pregnancy for a female patient with [redacted]
- Case [redacted] reported oligohydramnios and hyaline membrane disease complicated with sepsis and hypoglycaemia for the new-born associated with the maternal [redacted] exposure in case [redacted]

In both cases, the reporter concluded that the cause for these complications was unclear and the reporter causality for the cases should have been entered as 'unknown'. However, this causality assessment was incorrectly entered as 'not reported', and as company causality was assessed as 'not related', the cases did not trigger the reporting rules.

iii. The incorrect start date of 30 April 2021 from when [redacted] cases were considered

reportable by the MAH to the MHRA had been applied, which led to three serious [redacted] cases not having been reported to the MHRA.

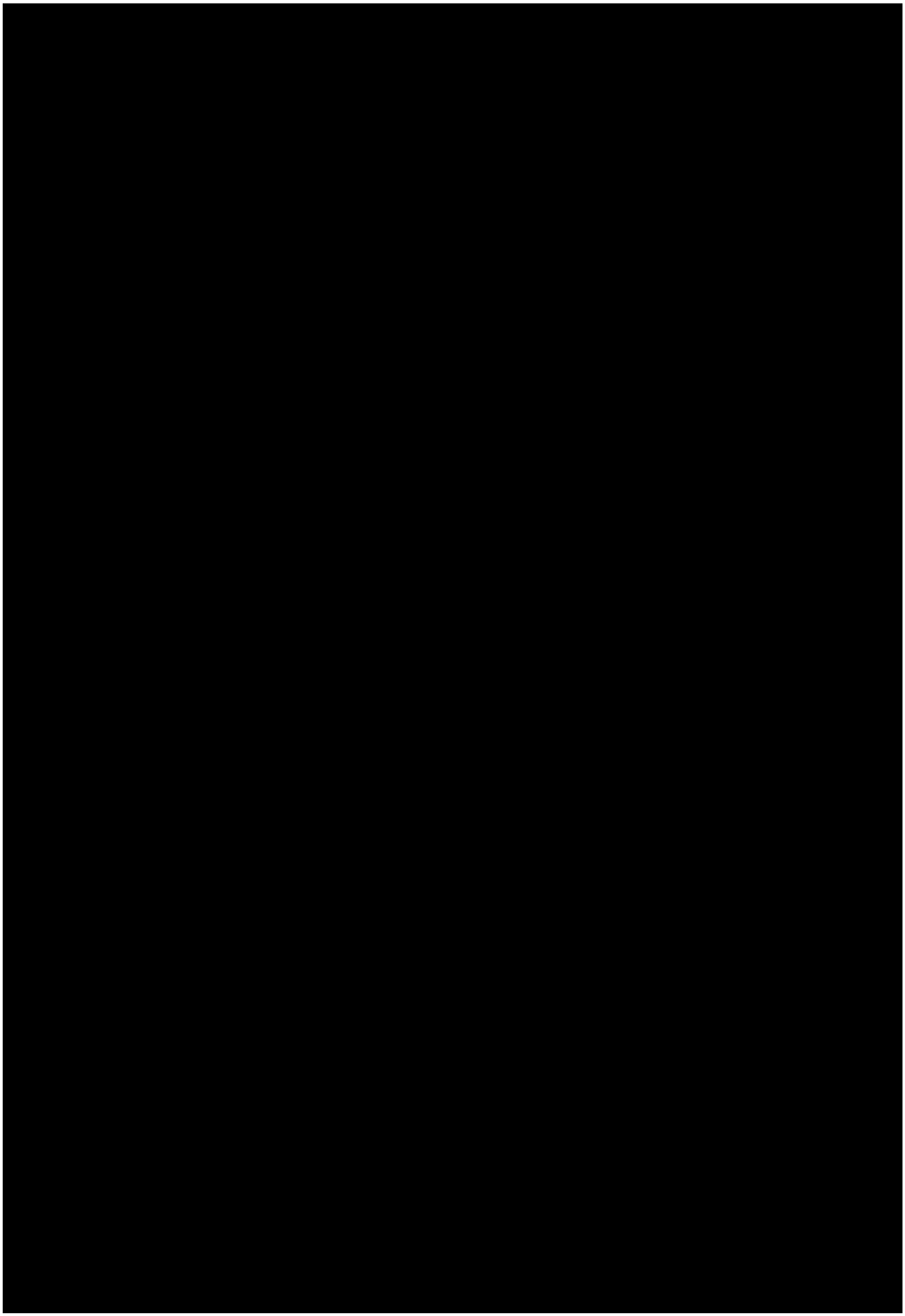
- [redacted] was a serious spontaneous case received from the Czech Republic on 12 April 2021, reporting vomiting, nausea and dyspnoea.
- [redacted] was a serious spontaneous case received from Germany on 14 April 2021, reporting atrial fibrillation.
- [redacted] was a serious report received from partner [redacted] on 09 March 2021, reporting dizziness, vertigo, fatigue, incorrect dosage administered and drug ineffective.

Roche raised a deviation [redacted] dated 14 June 2021) when 40 serious ICSRs were identified that had not been submitted due to a gap in updating the drug approval status list for the product. Within this deviation record, it was noted that ICSRs for [redacted] should have been submitted from 30 April 2021, an arbitrary date based on the "*payment and application date and not the submission date*" ([redacted] was assessed by the MHRA through a rolling review process). However, it is expected that qualifying ICSRs should be submitted to the MHRA from the date of rolling review commencement, when the first tranche of rolling data was submitted along with the application form. For [redacted] the first data package was submitted under this application route on 26 February 2021.

It is acknowledged that Roche attempted on 14 July 2021 to obtain confirmation from MHRA via the ABPI on the start date for ICSR submission for rolling review applications.

Root Cause Analysis

[redacted]



[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

[redacted]

Preventative Action(s)

[redacted]

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

Finding MA.1 b)
A non-conservative approach was applied to determine the reportability of literature cases originating from a solicited source if no reporter causality assessment was available, which led to valid cases not being submitted to the MHRA. Such literature cases could have arisen from solicited sources, for example non-interventional studies or registries. The MAH approach was that when such a literature case was received with no reporter causality, the MAH's causality assessment outcome was programmed to drive the reporting of the case. The MAH further explained that cases which originated from a literature source as either spontaneous or study type cases were processed depending on how the observations in the article had arisen. Specifically, the MAH stated: *"For literature articles arising from post-marketing studies; where there is an identifiable patient with an identifiable event but where the reporter has not indicated any suspicion of causality towards a given drug, the causality would be entered as "not reported". A company causality assessment will then be made, in the same manner as for other cases originating from ODCS [organised data collection scheme] sources, and if the company causality is Not Related, it is deemed that there is no reportable ADR and a case will not be submitted."* However, for such literature cases, despite the association with a solicited source of data, they should be handled as unsolicited cases, where the reporter causality assessment drives

reporting. Unless the reporter explicitly excludes causality between the event and product, these cases are reportable to EMA and/or MHRA. This position has been confirmed with the MHRA Patient Safety Monitoring team.

Due to the MAH's unconservative approach, a number of serious cases where no reporter causality assessment was reported were identified from the line listings which were not submitted to the MHRA, examples include:

- Case [redacted] received from the US on 15 October 2021, reporting events of septic shock, pneumonia, respiratory failure and NSTEMI resulting in death with [redacted]
- Case [redacted] received from Germany on 25 April 2022, reporting events of COVID-19 and a negative titre for SARS-CoV-2 antibodies post vaccination following treatment with [redacted]
- Case [redacted] received from Australia on 15 March 2022, reporting events of posterior tongue tie in an infant whose mother was treated with [redacted] prior and during pregnancy.
- Case [redacted] received from Australia on 15 March 2022, reporting events of mild transient respiratory distress which resolved spontaneously without specific treatment for an infant whose mother was treated with [redacted] prior to pregnancy.

Other examples to the above included cases [redacted] and [redacted]

Further consideration should also be given to the EMA 'Monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency - Inclusion and exclusion criteria for processing of Individual Case Safety Reports' (revision 1, effective date 21 December 2016). The MLM process described in section '2.6 Causality' (in the form of a flowchart), step 6.4.2, that if no causality was provided for a solicited literature case, to record the missing causality assessment and to progress to the next step (seriousness assessment) which results in processing the literature case as serious or non-serious ICSR. As a logical consequence, MAHs should follow the same approach so that consistency is achieved for the ICSRs deposited to EudraVigilance by EMA and MAHs.

It was also observed from the line listings that four cases ([redacted], [redacted] appeared to have been received from study literature cases with a reporter causality as 'Not reported' and company causality of 'Not related'. Yet these cases had been reported to MHRA and EMA, contrary to the MAH's explanation above.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]

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

Finding MA.1 c)

Several examples were identified where cases had been incorrectly reported to MHRA and EMA despite not meeting the minimum criteria of a valid ICSR.

i. UK case [redacted] was received from a Market Access Programme [redacted] and reported that 10 patients in the age group 2 months to 2 years were switched from [redacted] to another product due to efficacy concerns. No other AEs were reported, and no further patient identifiers were available to make this a valid ICSR. The case was submitted to the MHRA on 29 November 2021 despite not meeting the minimum reporting criteria

ii. UK spontaneous case [redacted] was received on 05 October 2020 reporting pregnancy with [redacted] Even though no adverse reaction was reported in the case, it was incorrectly submitted to EMA on 08 October 2020 and later on 18 November 2020, to add information that no further follow-up information was available. As reporter causality was entered as 'Not reported' instead of 'Not Applicable' in error, this triggered the EMA reporting rules at the time.

iii. Case [redacted] was received spontaneously on 03 April 2022 from Poland and reported a patient's "Death on day 5 after [redacted] administration" for a [redacted] While information on the disease development and biological markers was provided, there was no further information indicating that the death was considered to be causally related to [redacted]. The report was submitted to MHRA on 09 April 2022 despite only reporting an outcome.
The MAH explained that the report had been considered as related to [redacted] as it was received spontaneously. However, as no further information was provided about the clinical circumstances to consider the death as an ADR, and as the primary source did not indicate a possible causal relationship with [redacted], in line with GVP VI.B.2., this was not a valid ICSR.
The MAH conducted follow-up on 19 April 2022 to obtain the date of death and information on whether an autopsy was performed. However, further information on the cause of death and whether the reporter considered the death to be related to

[redacted] was not requested, which would have added meaningful information to the case.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

[redacted]

Corrective Action(s)
[redacted]

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

[redacted]

Preventative Action(s)
[redacted]

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

Finding MA.1 d)
Follow-up mechanisms had not been appropriately conducted for specific situations in order to collect the required information for the products. i. A case was identified for which no targeted follow-up questionnaire (TFUQ) was sent out even though the questionnaire was required as per the approved RMP. Spontaneous, serious case [redacted] was received from the US on 03 May 2022 for [redacted] and contained a report of a patient experiencing symptoms of [redacted] Follow-up was initiated by the MAH on 04 May 2022 but this only included the generic [redacted]

[redacted] not the [redacted] TFUQs as required in the [redacted] RMP. On 05 May 2022, follow-up information was received via the [redacted] stating that the physician did not believe that the patient had PML at that time.
The company [redacted] (effective July 2017), used to provide more information on when and how to use TFUQs, stated that "the [redacted] should be provided to the treating/reporting physician by the affiliate, along with the [redacted] immediately upon receiving a 'suspected [redacted] case' in the local IRT database." As per the memo, a suspected [redacted] case was defined at affiliate level as a *"case reporting a verbatim event term similar to one of the PTs from the c as follows:* [redacted]
The source documents for case [redacted] stated the patient reported "symptoms of [redacted] which should meet the definition of a 'suspected [redacted] case'.

ii. An example was identified where no follow-up was conducted for AE reports to obtain missing patient identifiers and the product batch number for the suspect biological product [redacted] was a spontaneous, serious case received on 17 September 2021 reporting a COVID-19 infection in a patient treated with [redacted] The initial report did not include any patient identifiers or the product batch number. While follow-up information was requested by Drug Safety on 21 September and 08 October 2021, this did not include any request for information regarding patient identifiers or product batch number. At the time of the inspection, no further follow-up information had been received.

iii. [redacted] was a spontaneous, serious case received on 05 April 2022 reporting pancreatitis with [redacted] via a Roche representative. Although this case was invalid as there were no patient identifiers, and there was no information on whether the reporter had consented to follow-up, follow-up was not conducted to obtain information on patient identifiers in order to validate the case if possible.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Preventative Action(s)

[redacted]

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

[redacted]

Finding MA.1 e)
A case for [redacted] was identified that had been submitted late to the MHRA. [redacted] was a serious case reported from the US for [redacted] initially received on 09 September 2020. The case reported the serious ADR of COVID-19 and was reported to EMA on 14 September 2020. Follow-up information was received on 11 September 2020 to update the event outcome to recovering/resolving, However, this new information was not reported to the MHRA until 03 February 2021, a delay of four months.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)

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

Finding MA.1 f)
Examples were identified of where the same AE report had been processed in separate cases in the GSDB which had not been identified during the duplicate check: i. A report was received on 30 March 2022 from [redacted] with a serious event of hemarthrosis with [redacted] The event was assessed as related by the reporter. Two cases were present in the GSDB for this report for the same patient: [redacted] and [redacted] Case [redacted] was reported to MHRA on 07 April 2022 but case [redacted] was not submitted as the reporter causality was incorrectly entered as 'Not reported' and company causality was also assessed as 'Not related'. ii. Case [redacted] received from the [redacted] EAMS via [redacted] (a web-based data capture and electronic import solution to capture structured AE data) on 28 May 2021 reporting the death of a patient was a duplicate of case [redacted] which was originally received from an MAH representative. While case [redacted] was reported to the MHRA due to the reporter causality being reported as 'Unknown' which was conservatively mapped to 'Related', case [redacted] was not submitted as the reporter assessed the underlying event leading to death as not related.
Root Cause Analysis
[redacted]

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Finding MA.1 g)
A number of case quality and coding deficiencies were identified on inspection: i. Incorrect source type had been assigned to cases within the GSDB: a. Case [redacted] originated from the [redacted] and was received from a business partner in the US on 14 October 2021. The case reported the serious AEs of dyspnoea, anxiety, pneumonia bacterial, acute respiratory failure, electrolyte imbalance, anaemia, pulmonary embolism and productive cough. No reporter causality was provided and the business partner had

assessed the events as not related.
As this case was received from the [redacted] it should not have been classed as spontaneous (with implied causality) within the GSBD but rather as a solicited case.
The MAH had self-identified this issue within finding [redacted] raised due to the incorrect coding of case type as spontaneous for reports received from the US [redacted] but case [redacted] was not included in the line listing generated on 20 January 2022 to support the corrective action.

b. Case [redacted] was received from the [redacted] US [redacted] on 22 November 2021 but had been incorrectly classified as a spontaneous case. The case was reportable to MHRA but had previously been missed (please refer to finding MA.1 a).
c. [redacted] was a literature case, with off-label use and no adverse events. Within the GSDB, the primary source was incorrectly classified as 'Literature - Non-Interventional Study/Program' and the programme number was assigned as [redacted], which reflected the case narrative which stated the patient was enrolled in this programme during the off-label use. However, there was no mention of the programme in the source data. Therefore, the case should have been processed as a 'Literature – Spontaneous' case.
d. [redacted] was a serious case identified from a US newspaper article reporting a medication error with [redacted] in 42 patients. The case was incorrectly assigned in the GSDB the protocol type [redacted] and classed as 'Literature - Non-Interventional Study/Program' when it should have been classed as a spontaneous case. As no ADR was reported in the article, the case did not qualify for regulatory submission.
e. Case [redacted] was received from the US on 10 September 2021 from a patient support services programme, PALS. The case reported serious events of gastrointestinal disorder, headache and fatigue with [redacted]
The case had been incorrectly classified in the GSDB as spontaneous rather solicited and as a result, no company causality assessment was conducted. This was defaulted to 'Not applicable' in accordance with the [redacted] User Manual. As the reporter had specified the causality for all respective events on the report form as 'Not applicable', no submission was triggered to MHRA. The MAH should confirm in the responses to the inspection report whether the case qualified for regulatory reporting after completion of the company causality assessment.
f. Case [redacted] for [redacted] was incorrectly assigned the primary source of clinical study with the protocol number 'UNKNOWN Open, non-company, CT' even though the source data stated that the case was received from compassionate use programme [redacted]. As per the [redacted] User Manual, Source section, this type of report should be coded as 'Non-Interventional Study/Program' with the correct protocol number. There was no impact for ICSR submission and inclusion in aggregate reports as both reporter and company causality was assessed as not related.

ii. Discrepancies were identified between the case narrative in the GSDB when compared to the source documentation:
   a. Case [redacted] was a spontaneous case received from the UK reporting pregnancy with [redacted] on 29 January 2021. The source documentation stated that '[redacted] Last infusion was 14/01/21. Date of positive pregnancy test 25/01/21" and stated the patient birth date. However, none of this information was captured in the structured fields in the GSDB or the case narrative.
   b. Case [redacted] was a solicited case from the US [redacted] received on 08 November 2021. The case was for a patient (aged 18 and above) who was one of three patients on the MAP who had not responded to [redacted]. The

following case coding quality issues were noted:

- The MAP programme number had not been entered into the structured database field.
- Reporter causality was coded as 'Not reported' and the narrative equally stated that the physician did not report a causality even though the source documentation listed the causality as unknown.
- The report narrative initially included reference to all three patients and in accordance with the [redacted] User Manual, separate cases had been created for the three patients. The cross-reference to the other cases was not included.

Roche corrected these deficiencies during the inspection on 15 June 2022.

iii. Case [redacted] was received from Italy on 26 March 2021 and reported the event of shivers for the patient after [redacted] infusion. Although this event was included in the case narrative, it was not coded in a structured E2B field in the GSDB. The case qualified for regulatory reporting but had not been submitted at the time of the inspection (please refer to finding MA.1 a).

iv. Cases were identified for which AEs had been coded incorrectly in the GSDB.

a. [redacted] was a serious spontaneous case received on 02 December 2021 from Italy. The case reported "sudden death, unknown causes" with [redacted] However, the event was coded as 'Death' only in the GSDB and reported as such to MHRA on 11 December 2021. In accordance with the MedDRA Points to Consider (release 4.21, March 2021), section 3.2.2 *"If the only information reported is death, select the most specific death term available."* The MedDRA dictionary contains a specific LLT for 'sudden death, cause unknown' that links to the PT of 'Sudden death' which should have been selected for this report.

b. Non-serious case [redacted] was received on 06 January 2022 from France reporting the prophylactic use of [redacted] This event was incorrectly coded as 'medication error' rather than 'off-label use'. In addition, a further event of 'drug ineffective' had been coded even though there was no evidence of this within the source documentation.

c. Non-serious case [redacted] was incorrectly entered as a valid literature case even though it did not contain any AEs. During case entry the statement from the article [redacted] was incorrectly assessed and processed as a report for lack of efficacy. This case had not been submitted to MHRA as it did not contain any patient identifiers.

Root Cause Analysis

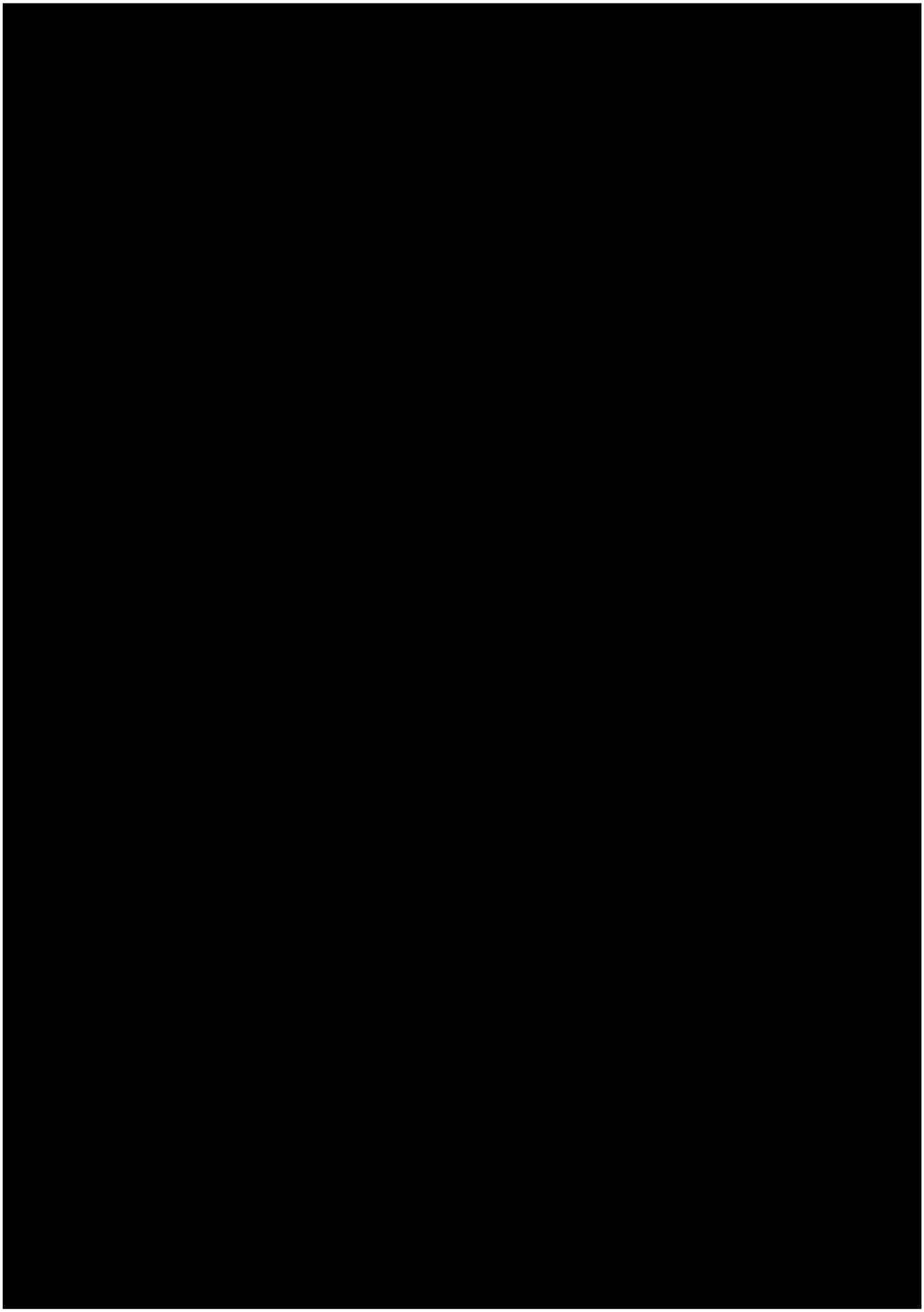
[redacted]

[redacted]

[redacted]

Further Assessment

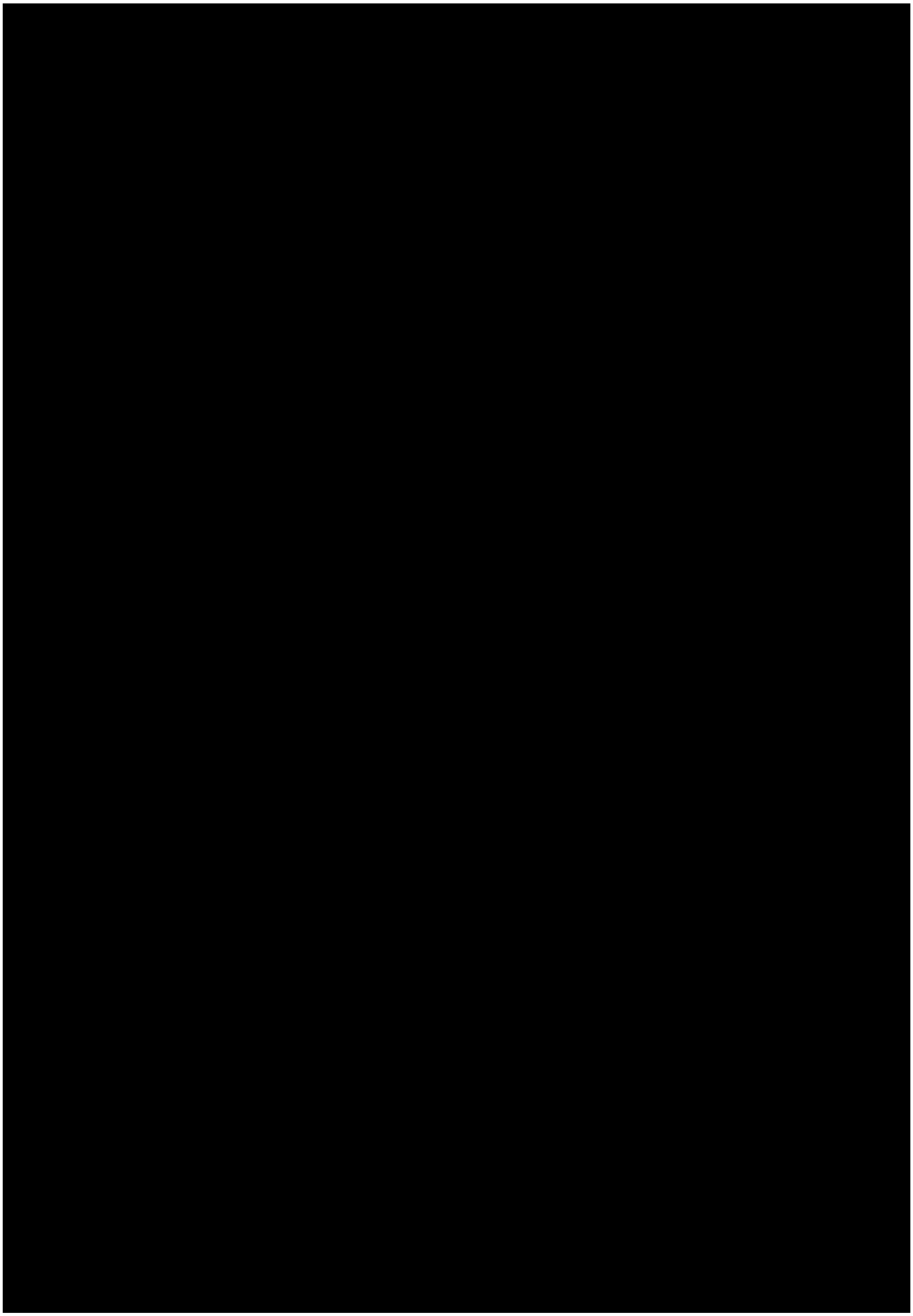
[redacted]



[redacted]

Corrective Action(s)

[redacted]



[redacted]

Preventative Action(s)

[redacted]

[redacted]

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

C.4.3 Minor findings

MI.1 Signal management

Finding MI.1a)
Signals for biological products were not routinely evaluated in the context of batch-specific exposure data. The [redacted] template specified the need for the Safety Scientist to evaluate whether a safety issue was related to a specific batch for certain situations such as: • an event reported in clusters • an event suspected to be related to a contamination of the drug product • where there was a change in the manufacturing process that may have impacted the safety profile of the product. However, signal evaluation had not been conducted to take account of batch-specific exposure data, in line with GVP Module P.II.B.4: *'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.'* As examples, the signal of angioedema/hypersensitivity and a signal regarding respiratory insufficiency for [redacted] were evaluated by the MAH, and neither were evaluated in terms of batch-specific exposure data.
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.1b)
There was a minor isolated discrepancy within the signal management tracker used by the MAH. The signal of elevated liver enzymes was identified from an FDA request received on 03 September 2021, and the signal was opened on 06 September 2021. The tracker stated that the signal had undergone validation and was deemed non-valid on the same day. However, the decision was actually taken on 28 September 2021. Signal validation had been conducted within stipulated SOP timeframes.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]

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

MI.2 Management and reporting of ADRs

Finding MI.2 a)

Further to finding MA.1g), additional errors were observed with case data entry within the GSDB which had minimal impact and were therefore graded as minor:

i. The company receipt date was incorrectly recorded for two cases in the GSDB:
   a. [redacted] was a spontaneous serious case from the UK, originally received on 13 November 2021 by an MAH representative. However the company receipt date recorded in the GSDB was 15 November 2021. There was no impact on regulatory reporting as the case was fully processed in the safety database on 19 November 2021.
   b. Case [redacted] was a spontaneous serious case from the UK, originally received on 05 April 2021 by an MAH representative. However, the company receipt date recorded in the GSDB was 06 April 2021. There was no impact on regulatory reporting as the case was fully processed in the safety database on 09 April 2021.

ii. Eight cases* received from the [redacted] US [redacted] had not been updated in the GSDB to reflect the correct version of the protocol name for the programme. The protocol name for the previous programme title was [redacted] also linked to the incorrect primary source of 'clinical study'. The correct title for the programme which the cases should have been updated to was [redacted] The MAH confirmed that the different protocol name did not impact on the inclusion of the one affected serious ICSR [redacted] in the [redacted] PBRER [redacted] as it was received prior to IBD (19 July 2021) in March 2021. As the remaining seven cases were non-serious, there was no impact on ICSR submissions to the MHRA. Case [redacted] qualified for regulatory reporting but was not submitted (also refer to MA.1 a) iii.).
   [redacted]

iii. 15 cases did not have the 'Initial unit type' field completed in the GSDB, used to prevent cases received from business partners or regulatory authorities being resubmitted back. In accordance with the [redacted] User Manual [redacted] General Tab – Admin Section:
   "This field can be used in submission rules to ensure that information sent from

a Business Partner or Regulatory Authority to Roche is not resubmitted back to the same sender. Therefore, the [redacted] user must assess the sender of the information at each version to verify where the report was received from to prevent submission of the same information to the original sender if the case qualifies for submission."

Out of the 15 cases, one case [redacted] was received from business partner [redacted] which meant that the case was resubmitted to this business partner. For all other cases, there was no impact of this field being incomplete as they were received from non-business partners or non-regulatory authority sources.

Root Cause Analysis

[redacted]

[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)
Minor errors were contained within the line listing provided for the purpose of inspection: i. Four [redacted] cases - [redacted] – had a blank 'suspect product name' whereas within the GSDB, this field was completed within the case. The MAH explained that this was due to the drugs [redacted] being incorrectly selected from the DRL. As a result, the preferred WHO Drug Dictionary decoding field did not populate when these product codes were selected from the DRL. None of the affected cases qualified for regulatory reporting but as part of the responses to the inspection report, the MAH should confirm the impact of the blank 'suspect product name' on the inclusion of these cases in signal detection activities and PBRERs. ii. Within the line listing, cases [redacted] were listed as related to an identifiable patient. When questioned as to why these cases (which appeared to meet the reporting criteria to the MHRA or EMA) were not submitted, the MAH explained that both cases arose from a Summary Report and concerned a group of patients, from which it was not possible to identify which individual patient experienced the AE. Therefore, it was not possible to validate the cases for regulatory reporting.
Root Cause Analysis
[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]	

MI.3 Sources of safety data

Finding MI.3 a)
There was an isolated example of a case reporting use of a product during pregnancy had not been reported to UK Drug Safety for inclusion in the GSDB. UK Medical Information teams at the MAH received a case on 26 February 2021 detailing a

patient exposure to [redacted] during pregnancy and an outcome that the pregnancy would be aborted. As the enquirer had mentioned they did not wish to report to Roche but rather through the YellowCard directly themselves, Medical Information did not report this case to UK Drug Safety.

This is not in line with GVP Module VI.B.6.1. which states:
"Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data, or reports which have a normal outcome should not be submitted as ICSRs since there is no suspected adverse reaction (see VI.B.2. for ICSR validation). These reports should however be collected and discussed in the periodic safety update reports […]."

Once this was raised on inspection, Medical Information took the corrective action and reported the case to UK Drug Safety for onward processing on 16 June 2022.

Root Cause Analysis

[redacted]

[redacted]

Corrective Action(s)

[redacted]

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MI.3 b)
The following deficiencies were identified with case transfer verification (CTV), used as a means of reconciliation, between the MAH and relevant third parties: i. There was an example of a compassionate use programme (CUP) for which CTV had not been completed. For [redacted] although CTV had been requested by the MAH, no response had been provided. As there was no guidance at the MAH for how many follow-up attempts should be made or escalation processes for failure to adhere to CTV agreements, CTV remained outstanding. The MAH are requested as part of further assessment to identify any other CUPs where CTV had not been undertaken or completed in line with SDEAs. ii. In accordance with the SDEA with the sponsor for the investigator-initiated study [redacted] CTV was due to be completed monthly. However, CTV had not been completed since December 2021. There was no evidence of follow-up or escalation of this until May 2022 after which a line listing was received on 27 May 2022, which confirmed that no AEs had been missed. iii. CTV acknowledgement was delayed for investigator-initiated study [redacted] The sponsor had sent the monthly CTV on 05 January 2022 but this was not acknowledged by the MAH until 01 March 2022. As no AEs were received by the sponsor in December 2021, there was no impact due to this delay.

Root Cause Analysis
[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

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

MI.4 Pharmacovigilance System Master File

Finding MI.4

Minor discrepancies were noted with the PSMF [redacted] dated 06 May 2022:

i. CUPs were included within the PSMF Annex [redacted] incorrectly:
   - CUP [redacted] was ongoing in the UK, but the UK was not listed as a country.
   - The following CUPs were included as ongoing, but the MAH confirmed that these CUPs were not ongoing in 2022: [redacted]

ii. A CAPA that was closed for [redacted] (a major finding identified from an audit of business partner [redacted] was erroneously included within the PSMF [redacted] pending CAPA plans. Actions had been implemented as part of the CAPA prior to the end of 2020 but as the effectiveness check had not been completed within the [redacted] documentation, the CAPA remained visible within the PSMF.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

MI.5 Management of deviations and CAPA

Finding MI.5
Delays were identified in actioning corrective actions related to deviations within the PV system: i. There was a delay of one month of sending a reminder to TCS case processing staff regarding the correct case type and protocol number for cases received from the [redacted] US [redacted]. As detailed in self-identified finding [redacted] the reminder was due to be sent by 31 January 2022 but it was only sent on 01 March 2022. ii. The completion date for corrective action [redacted] for major self-identified finding [redacted] (delayed reporting of some [redacted] cases to the MHRA) was incorrectly entered into [redacted] (the Roche quality event system) as 01 March 2022. However, the action to remind the UK regulatory affairs team of the relevant MA applications

and variations that require notification to the UK safety team was completed on 16 December 2021.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

MI.6 Vendor oversight

Finding MI.6
Standalone quarterly teleconferences between TCS and the MAH UK LSU were not conducted in Q2, Q3 and Q4 in 2021 as required by the [redacted] effective date 20 April 2022), [redacted] The purpose of the quarterly teleconference was to review the overall project and discuss issues, including the review of metrics. The MAH explained that the quarterly meeting for the UK LSU was not scheduled for Q2 and

Q3 2021 as any issues and project status were discussed in the ongoing bi-weekly meetings between TCS and the UK LSU. In addition, the overall quarterly quality performance (including those from the UK LSU) was presented in the quarterly [redacted] meetings. A deviation regarding the missed meetings for Q2 and Q3 2021 was only raised by TCS [redacted] on 01 April 2022. As part of the corrective actions, the metrics produced by TCS for the above mentioned quarters were presented to the UK LSU on 26 May 2022, which also covered the Q1 2022 metrics.
[redacted]
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

C.4.4 Comments

1. Management of ADRs: Case [redacted] was coded with a reporter country of Ukraine even though it was received from license partner [redacted] based in the US. The received CIOMS I form stated in the narrative [redacted]

[redacted] It is acknowledged that the country was already stated as Ukraine in the original report received from [redacted] However, where there is obvious illogical information this could be raised and clarified with the partner. The case was received on 09 March 2021 but was not submitted to MHRA (also refer to MA.1 a) iii.)

Company Response: *Prior to the acquisition of [redacted] the partner's pharmacovigilance department was responsible for the submission of safety reports to the appropriate Health Authorities. Upon review of the CIOMS received for [redacted] the reporter was said to have purchased 5 doses of the product from a physician in Israel who agreed to send it to the Ukraine. It was also specifically stated within the CIOMS that this route of obtaining the product was under investigation by [redacted] because the product had not been approved in Israel nor Ukraine at that time. No further information with regards to the outcome of this investigation was provided at the time of the initial report, however, the case was processed by [redacted] under the [redacted] Follow-up was performed by [redacted] and contact was eventually made after several failed attempts. Other than providing further information on the progress of the patient, the reporter refused to answer any additional questions.*

2. Medical Information: Medical enquiries were responded to directly in the system [redacted] and responses were retained within that system. However, when responses were sent out by internal company staff, such as medical assistance personnel, these were not necessarily retained. As evidenced in medical information case [redacted] for which an AE was reported, the response was sent out by a medical assistance team member through their work email [redacted] but due to the retention policy of Gmail (90 days only) the response email was no longer available. Roche should consider the traceability of such evidence when related to an AE to have assurance of what information was provided to the enquirer and the information that might have been shared about the relevant AE.

Company Response: *This comment will be captured in the local UK risk register for review and assessment by the Local Medical Compliance Committee.*

3. Solicited sources of safety information: During the solicited sources of information interview session, it was described that there were a number of safety measures employed to ensure market research and patient support programmes, investigator-initiated studies and CUPs were flagged to Drug Safety to ensure that appropriate SDEAs were in place and being adhered to. However, it was confirmed that these were not written in formal procedures and it is recommended that these processes are documented to reflect current practices.

Company Response: *This comment will be captured in the local UK risk register for review and assessment by the Local Medical Compliance Committee.*

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.

It is requested that a brief post-inspection CAPA update be provided in due course for MA.1 b), where the MAH will be communicating with the EMA regarding the handling of literature cases originating from a solicited source.

APPENDIX I REFERENCE TEXTS

- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916) as amended.
- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP).
- Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority.
- CPMP/ICH/377/95: ICH guideline 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: ICH guideline E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: ICH guideline E2E "Pharmacovigilance Planning".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	123abc abc	**DATES**	13 – 16 June 2022
PHARMACOVIGILANCE INSPECTION OF	roche Roche	**START TIME**	09:00
LOCATION	Day 1: Remote Days 2 - 4: Onsite (6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW) Insert inspection address	**INSPECTION TEAM**	[redacted]

This inspection will be primarily focused on a review of the following topics:

- Spontaneous sources of safety data
- Solicited sources of safety data
- Management of ADRs
- Signal management
- Periodic safety update reports (PSURs)

The inspection plan below outlines the topics for which specific sessions are requested to orientate inspectors around the systems and processes in place. Additional ad hoc discussions with company personnel may also be required. Access to view live systems such as the safety database or systems used in the activities under review may also be requested. Please ensure that subject matters experts are available and indicate any times personnel may be unavailable in the below. The lead inspector will liaise with the designated inspection host to arrange ad hoc discussions as required.

The remainder of the inspection will consist of document review and further document requests will be submitted throughout the course of the inspection.

Monday, 13 June 2022 (Day 1, remote)

Opening Meeting (via videoconference)

09:00 BST, led by the lead inspector

The agenda will be as follows:

1. Review of scope and arrangements for the inspection (lead inspector)

2. Brief presentation by Roche (~20 mins) with an overview of the company and pharmacovigilance system. The presentation should focus on the topics listed for inspection and any relevant ongoing remediation work in the pharmacovigilance system. Please also highlight any significant changes to the pharmacovigilance system since the last MHRA inspection. The remainder of the day will consist of remote document review by the inspectors. Additional document requests may be submitted to Roche throughout the day.	
Tuesday, 14 June 2022 (day 2, onsite)	
Inspection room 1 - Provisionally 11:00 BST **Spontaneous sources of safety information**, including but not limited to: • Medical information in the UK • Product quality complaints in the UK • Management of PVAs	Interviewee(s): • [redacted] UK Licence to Operate (LTO) Partner- Medical Information • [redacted] UK LTO Partner- Quality • [redacted] UK LTO Partner- Safety • [redacted] [redacted] Global Process Owner - Pharmacovigilance Agreements, Product Development Safety Risk Management (PDS) • [redacted] Group Head PV Partnering, PDS
Inspection room 2 - Provisionally 11:00 BST **Management of ADRs**, including but not limited to: • Case quality in the safety database, submission to MHRA and follow-up activities • Global safety database configuration • Quality assurance and oversight activities • Remediation of deviations	Please could a brief presentation (no more than 15 min) be prepared to provide an overview of: • Case processing steps from data entry to regulatory submission • Safety database configurations • Quality assurance and vendor oversight activities Interviewee(s): **Global Process Owner** • [redacted] Global Process Owner (GPO) ICSR Case Processing, PDS **Case Quality in the safety database & submissions (global)**

	• [redacted], ICSR Case Processing Business Process Owner (BPO), PDS • [redacted] ICSR Intake & Submissions BPO, PDS **Case Quality in the safety database and submissions (UK local)** • [redacted] UK LTO Partner- Safety **Follow-up Activities** • [redacted] UK LTO Partner- Safety **Global Safety Database Configuration** • [redacted] PV Intelligent Automation & Business Systems Solutions, PDS • [redacted] Delivery Service Manager, Product & Services Management Chapter, Product Development Informatics (PDIX) **Oversight Activities** • [redacted] Safety Operations Vendor Interface (OVI), PDS • [redacted], UK LTO Partner- Safety **Remediation of Deviations** • [redacted] Global Process Quality Responsible (GPQR), PDS **Quality Assurance** • [redacted], Principal Quality Lead, QA Process-GVP, Product Development Quality (PDQ)

Inspection room 1 - Provisionally 14:00 BST **Solicited sources of safety data**, including but not limited to collection of safety information and management of: • Investigator initiated studies • Compassionate use programmes • Patient support programmes	Please could a brief presentation (no more than 10 minutes) be prepared to provide an overview of the receipt of safety data from solicited sources in the UK. Interviewee(s): • [redacted] UK LTO Partner- Safety • [redacted] LTO Partner-Safety • [redacted] UK MAP Lead and UK LTO Partner-Safety • [redacted] UK PV Approver and UK LTO Partner-Safety
Wednesday, 15 June 2022 (Day 3, onsite)	
Inspection room 1 - Provisionally 10:00 BST **Signal management**, including but not limited to: • Detection, validation, evaluation and tracking of signals • Oversight activities	Please could a brief presentation (no more than 10 minutes) be prepared to provide an overview of signal management activities. Interviewee(s): • [redacted] Signal Management GPO, PDS • [redacted], Signal Detection BPO, PDS • [redacted], UK LTO Partner- Safety

Inspection room 2 – Provisionally 10:00 BST **PSURs**	Please could a brief presentation (no more than 10 minutes) be prepared to provide an overview of PSUR preparation, quality and oversight aspects. Interviewee(s): • [redacted] Aggregate Reporting GPO • [redacted] Clinical Safety, PDS • [redacted] Regulatory Reporting, PDS • [redacted] Safety Analytics & Reporting, PDS • [redacted] UK LTO Partner- Regulatory

Thursday, 16 June 2022 (Day 4, onsite)

The remainder of the inspection will primarily consist of document review with ad hoc discussions if required.

The inspection will finish with a closing meeting on Day 4 (time to be confirmed) when verbal feedback will be provided from the inspection. All relevant personnel are welcome to attend the closing meeting.

Contact point and opening meeting attendees

A designated contact point should be provided who can assist with any questions from inspectors or arrange ad hoc discussions between inspectors and subject matter experts if required.

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

Designated contact point: [redacted] *Head QA Process- GVP, Product Development Quality,* [redacted]

Opening meeting attendees:

- [redacted] *General Manager, UK Affiliate (Roche Products Limited),* [redacted]
- [redacted] *Chief Medical Officer, UK Affiliate,* [redacted]
- [redacted] *Medical Affairs Chapter Lead, UK Affiliate,* [redacted]
- [redacted] *License to Operate (LTO) Chapter Lead, UK Affiliate,* [redacted]
- [redacted], *UK QPPV, UK Affiliate,* [redacted]
- [redacted] *Deputy UK QPPV, UK Affiliate,* [redacted]

- [redacted] *Local Quality Responsible, UK Affiliate,* [redacted]
- [redacted], *EU QPPV,* [redacted]
- [redacted] *Global Head of Early Development, Late-stage & Marketed Medicines Safety,* [redacted]
- [redacted] *Global Head of Drug Safety Operations,* [redacted]
- [redacted] *Head QA Process- GVP, Product Development Quality,* [redacted]
- [redacted] *Principal Quality Lead, QA Process- GVP, Product Development Quality,* [redacted]
- [redacted] *Principal Quality Lead, QA Programs, Product Development Quality,* [redacted]

N.B. The inspection plan may need to be amended during the inspection.

APPENDIX III AD HOC DISCUSSION ATTENDEES

Day/Time	Inspector	Topic	Attendee Name, Job Title
Tuesday, 14-Jun-2022, 15:00	[redacted]	B15 Listing	• [redacted] Global Process Owner (GPO) ICSR Case Processing, PDS • [redacted] Business Systems Owner, PDS • [redacted] Safety Data Transformation Lead, PDS
Wednesday, 15-Jun-2022, 13:30	[redacted]	Signal Detection Walkthrough	• [redacted], Signal Management GPO, PDS • [redacted] Signal Detection BPO, PDS
Wednesday, 15-Jun-2022, 13:30	[redacted]	Follow-up on [redacted] & [redacted]	• [redacted] Global Process Owner (GPO) ICSR Case Processing, PDS • [redacted] Senior Safety Director (PBRER SME), PDS • [redacted] Global Process Quality Responsible (GPQR), PDS • [redacted], Aggregate Reporting GPO • [redacted] UK LTO Partner Safety • [redacted] UK QPPV
Thursday, 16-Jun-2022, 09:15 am	[redacted]	Roche requested discussion on U3/U4	• [redacted] Senior Safety Director, PDS
Thursday 16-Jun-2022, 11:00am	[redacted]	Review of signal tracker (B22)	• [redacted], Signal Detection BPO, PDS
Thursday 16-Jun-2022, 12:30pm	[redacted]	Questions on I6, H3, and targeted follow-up for LoE in US for [redacted]	• [redacted]**lan,** Senior Process Director & Global Process Owner (GPO) ICSR Case Processing • [redacted], Safety Data Transformation Lead • [redacted] UK LTO Partner, Safety

Thursday 16-Jun-2022, 1:45pm	[redacted]	Follow up on Med Info responses	• [redacted], UK License to Operate (LTO) Partner- Medical Information
Thursday 16-Jun-2022	[redacted]	Follow-up attempts for 2 pregnancy cases	• [redacted] UK LTO Partner- Safety