Medicines & Healthcare products
Regulatory Agency

PHARMACOVIGILANCE
INSPECTION REPORT

Pharmacovigilance System Name:	Laboratorios Farmacéuticos ROVI, S.A.
MHRA Inspection Number:	Insp GPvP 15406/6564-0001

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AGEP	Acute Generalized Exanthematous Pustulosis
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CPD	Company Product Dictionary
DCP	Decentralised Procedure
DME	Designated Medical Events
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EU	European Union
GVP	Good Vigilance Practice
GPVL	Global Pharmacovigilance Level
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
[redacted]	[redacted]
LPVL	Local Pharmacovigilance Level
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
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
PT	Preferred Term
PV	Pharmacovigilance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan

RMS	Reference Member State
RSI	Reference Safety Information
SAE	Serious Adverse Event
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection
System(s) inspected:	Laboratorios Farmacéuticos ROVI [redacted]
Site(s) of inspection:	Remote
Main site contact:	[redacted] Julián Camarillo, 35 28037, Madrid Telephone: [redacted] Email: [redacted]
Date(s) of inspection:	12 – 15 December 2022
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted] (observer from the TGA)
Previous inspection date(s):	N/A
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Products selected to provide system examples:	• [redacted]
Name and location of UK QPPV:	[redacted] Julián Camarillo, 35 28037, Madrid Telephone: [redacted] Email: [redacted]
Global PV database (in use at the time of the inspection):	[redacted] commercially available
Key service provider(s):	Not applicable – all pharmacovigilance activities are performed by the MAH
Inspection finding summary:	0 Critical findings 4 Major findings 5 Minor findings
Date of first issue of report to MAH:	18 January 2023
Deadline for submission of responses by MAH:	22 February 2023 03 April 2023
Date(s) of receipt of responses from MAH:	22 February 2023 03 April 2023
Date of final version of report:	13 April 2023
Report author:	[redacted] Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Laboratorios Farmacéuticos ROVI, S.A. 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.

Laboratorios Farmacéuticos ROVI, S.A. (hereafter referred to as ROVI) is a Spanish, family-owned pharmaceutical company that has been in existence for over 70 years. The company specialised in development of [redacted]) and has three such medicinal products authorised in the UK: [redacted] tradenames of [redacted] and [redacted] were first authorised in the UK on [redacted] under the decentralised procedure (DCP) with Germany as the reference member state (RMS). Of the [redacted] only [redacted] s currently marketed in the UK and this biological product (a biosimilar) is on the MHRA additional monitoring list.

ROVI's headquarters are in Madrid, Spain, where global PV activities (GPVL) are based. ROVI has several affiliates across Europe, including the UK, and all pharmacovigilance (PV) activities have been delegated to GPVL. Local PV level (LPVL) units act as the local contact persons for PV and these units are responsible for the collection and collation of safety information in that region.

B.2 Scope of the inspection

The inspection included a review of the local UK and global PV systems and was performed remotely. Personnel from GPVL and the local LPVL unit were available throughout the inspection and participated in ad hoc discussions held via videoconference.

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

The PSURs and the quality management system were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent PV inspection.

B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 30 June 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 the pre-inspection requests is contained within document request sheets A and B.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan.

A closing meeting was held to review the inspection findings on Thursday 15 December at 4.40 pm.

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

Not applicable as this was the first MHRA pharmacovigilance inspection of the company.

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 Signal management

Requirements:

GVP Product- or Population-Specific Considerations II: Biological medicinal products (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)

P.II.B.4. Signal management
"Signal detection for biologicals should therefore be specific to the product, as well as the active substance. All steps of signal management should be performed at the level of the product name, as well as the active substance. In case of a signal any effort should be made to identify any common root cause such as batch.
Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological and important differences between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change).
[…]
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."

GVP Module IX – Signal management (Rev 1) (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)

IX.B.5. Quality requirements
"Signal management is considered a critical process (see GVP Module I). Any signal management system should be clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardised, that these tasks are conducted by staff with appropriate qualifications and expertise and that there are provisions for appropriate control and, when needed, improvement of the system. A system of quality management (see GVP Module I) should be applied to all signal management processes. Detailed procedures for this quality system should be developed, documented and implemented."

GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (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)

IX. Add I.3.1. Designated medical events
"It is recommended that these designated medical events (DME) are drawn to the attention of signal detection assessors irrespective of any other statistical methods used and that they are prioritised for clinical review."

ROVI's GPVL conducted signal management activities in house for all products. Detection activities included a review of the safety database where ADRs would be analysed for each detection period, and a quantitative analysis of labelled AEs and qualitative analysis of unlabelled AEs would occur. Fatal cases would independently be assessed. Analysis was also conducted for data included within EVDAS. For [redacted] signal detection was carried out every three months (quarterly).

A number of deficiencies were identified with the signal management processes at ROVI.

Finding MA.1 a)

The signal management processes at ROVI did not meet the requirements for biological products as specified in GVP PII. [redacted] is a biosimilar product and therefore the requirements in GVP PII apply.

i. There were no processes in place to detect any acute and serious new risks that may emerge following a change in the quality of a biological, whether that originated from differences between batches of the same product or unanticipated changes in the manufacturing process.

ii. There were no processes in place to ensure all steps of signal management were performed at the level of the product name, as well as the active substance. ROVI were MAH to two [redacted] products: [redacted]i (marketed in the UK) and [redacted] (not marketed in the UK).

iii. There were no processes in place to ensure signals for biological products were evaluated in the context of batch-specific exposure data. To note, only one signal had been identified for [redacted] at the time of the inspection, and this was an update requested by CHMP following a PSUR assessment. As this signal had been validated and confirmed by PRAC it did not require further evaluation by ROVI.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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

Finding MA.1 b)

Quarterly periodic detection reports produced for [redacted] did not include accurate, up-to-date data within the cumulative data set presented in these reports.

Periodic detection reports were produced quarterly by extracting ADR data from the safety database covering the timeframe for the review period. Cumulative data from the safety database was reviewed using [redacted] effective 13 June 2022) [redacted] This was an [redacted] spreadsheet that logged the number of AEs (count of PTs) for each SOC by review period and was conditionally formatted to flag any PT that had a significantly increased frequency (one standard deviation above the mean count of previous periods).

Data was manually added each quarter to the spreadsheet for the current review period only. As such, any updates to ADR data for reports received prior to the current review period would not be reflected on the spreadsheet. For example, if a case was significantly changed through amendment or addition of event PTs, nullified or deleted, there was no process to alter the

data that had already been added to the sheet. This impacted both the assessment of cumulative totals of AEs and the conditional formatting used to identify significant increases in frequencies for events. Although no direct examples were identified on inspection, it is likely that errors exist within the data set since some cases will have been updated from when they were first added to the spreadsheet. ROVI should ensure that going forwards the data included for previous review periods is up to date to ensure cumulative signal detection is based on accurate 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 MA.1 c)

The procedures governing the signal management processes lacked sufficient detail for specific stages of signal management.

i. There was insufficient detail on when signals detected through quantitative and qualitative analysis would be taken forward for signal validation. [redacted] effective 13 June 2022) section [redacted] stated: *"If a possible signal is identified with a low risk in*

terms of seriousness, frequency or impact, [redacted] *[signal validation form] will not be required and the signal will be tracked only in* [redacted] *for next period monitoring".*

Despite this procedural guidance, an example was identified on inspection of a possible signal that had been detected for [redacted] concerning a serious ADR which had been tracked for the next monitoring period rather than considered for signal validation. DRESS syndrome was identified as a possible signal in the periodic detection report dated 01 October 2021 – 31 December 2021, where it was decided that the event would be closely monitored in future reports. DRESS syndrome is included on the EMA's Designated Medical Event (DME) list, which documents serious medical concepts often causally associated with drugs. During the inspection, ROVI stated that this event was considered low risk in terms of frequency; however, this is a rare reaction and considering the number of ADR reports received by ROVI for the product, this is not considered to be a valid reason for considering this possible signal 'low risk'. At the time of the inspection, ROVI had not taken forward any possible signal for validation that had been identified through their quantitative or qualitative analyses. Consequently, as part of the actions taken to address this finding it is recommended that ROVI reassess the suitability of signal validation thresholds as a result.

As part of the CAPA responses, ROVI must also revisit the possible signal of DRESS to ensure this has been properly assessed in light of the above points and to determine if validation is required. If ROVI consider that validation is not required, please provide the rationale.

ii. [redacted] effective 13 June 2022) section [redacted] stated: *"If a possible signal is identified with a low risk in terms of seriousness, frequency or impact,* [redacted] *[signal validation form] will not be required and the signal will be tracked only in* [redacted] *for next period monitoring".*

The length of time for which these events should be monitored was not defined in any corresponding work instruction or periodic detection report. [redacted] to the SOP listed possible signals that had been monitored for varying lengths of time. As examples this included anaemia which was rejected after monitoring for 12 months, night sweats for six months and subdural haematoma for three months. However, there were no supporting instructions on how the monitoring frequency should be decided upon. As such, two signals in [redacted] where monitoring was ongoing at the time of inspection had no defined monitoring endpoint - monitoring was to continue to the next period and only ended at an undefined time when a rationale was decided upon.

It is important that the timeframe for monitoring takes into account the number of ADR reports received for individual products, as this will impact on the probability of receiving reports of the same events and subsequently taking forward a possible signal to validation.

It was also noted that section [redacted] of [redacted] effective 13 June 2022) should be updated at the next available opportunity to include the requirement that emerging safety issues (ESIs) should be notified to the MHRA, as well as the EMA, within three working days. It is acknowledged that section [redacted] details the MHRA submission requirements but this should be clear throughout the SOP.

Root Cause Analysis

[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]	

Finding MA.1 d)
An error was identified in the [redacted] periodic detection report for the period 01 July 2022 – 31 September 2022.

In the table documenting unlabelled adverse events, two reports of drug reaction with eosinophilic systemic symptoms were listed. In the column 'Previously monitored? (Y/N)', it stated 'N' (no). However, this event was previously monitored between January 2022 – June 2022.

During the inspection, ROVI confirmed that there was no impact on the signal detection assessment for [redacted] as this possible signal had been closed due to the receipt of no further cases in the two subsequent monitoring periods and the two cases received in the current period were not considered related to [redacted] administration.

To note, this is a minor finding but included in this section of the report within the relevant topic area for continuity.

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]	

MA.2 Maintenance of reference safety information

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916)

Part 5 Marketing Authorisations, Regulation 76
"(1) The holder of a UK marketing authorisation for a medicinal product must ensure that the product information relating to the product is kept up to date with current scientific knowledge."

Part 16, Regulation 327: Powers of inspection, sampling and seizure
"(1) An inspector may inspect anything mentioned in paragraph (2) –
[…]
(g) information and documents relating to the safety of medicinal products or active substances, including information and documents relating to compliance with — […]
(ii) the requirements of Part 11 (pharmacovigilance),
[…]
(vi) obligations under regulations 75 (obligation to provide information relating to safety) and 76 (obligation in relation to product information)"

When new information about the benefits and risks of a product become available it may be appropriate to make changes to reference safety information (RSI) documents, such as summary of product characteristics (SmPCs), and patient information leaflets (PILs) so that healthcare professionals or patients are able to use the medicinal product correctly on the basis of full and comprehensive information. This in turn should be implemented into product packs to ensure that information can be accessed by those taking and prescribing the medication.

Finding MA.2 a)

There were no documented procedures that described the processes for implementing updated product information in a timely manner.

It was confirmed on inspection that the relevant SOPs regarding maintenance of product information governed by the PV department [redacted] effective from 07 November 2022)) and also those under the responsibility of regulatory and manufacturing teams lacked the necessary detail to ensure SmPCs and PILs could be implemented in line with MHRA expectations. Specifically:

- There were no documented procedures to describe the timeline of implementation of updated PILs into product packs following approval by the competent authority. The MHRA's expectation is that following approval, updated PILs should be introduced into product packs within three to six months. To note, that for safety variations submitted as a Type IAIN, MHRA approval is not required and the PILs should be implemented within three to six months of submission of the variation.
- There were no documented procedures to describe the update of the EMC website following safety updates to the SmPC and PILs despite the EMC being used by the MAH as a platform to host product information. The MHRA's expectation is that following approval of updated product information, the EMC should be updated with the new versions within ten days.
- There were no documented procedures to describe the process and timelines for sharing updated product information with relevant third parties in a timely manner. The MHRA's expectation is that stakeholders should be sent copies of updated product information following company implementation within ten working days.

As maintenance of product information is a critical PV process, the supporting documented procedures must include sufficient detail for all steps of the process. Although the lack of detail in procedures was noted as part of [redacted] raised from the PV audit conducted 15 – 17 November 2021, the corrective action *"Describe the process for safety variations communications and implementation in Rovi SOPs"* (closed 30 June 2022) was not addressed (see finding MI.4 a) i. a)). At the time of inspection, only one safety variation had been identified, which was still awaiting MHRA approval prior to implementation.

To note, the MAH did not provide the corresponding SOPs held by regulatory and manufacturing teams as they considered these outside the scope of the inspection (not pharmacovigilance related). However, this is incorrect as the procedures requested related to patient safety (implementation of product information) and should have been provided.

Root Cause Analysis

[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]	

MA.3 The pharmacovigilance system master file

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11, Regulation 182
"(2) The holder must (as part of its pharmacovigilance system) –
(b) maintain and make available on the request of the licensing authority a pharmacovigilance system master file and ensure it is permanently and immediately available for inspection electronically in the United Kingdom at the single point from which the reports referred to in regulation 187(4) are accessible."

GVP Module II – Pharmacovigilance system master file (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)

II.B.4.8. Annex to the PSMF
"An annex to the PSMF must contain the following documents:
• A list of medicinal products nationally authorised in the UK covered by the PSMF, including the name of the medicinal product, the international non-proprietary name of the active substance(s) and the specific region of the UK in which the authorisation is valid […]
The list of medicinal products authorised in the UK should also include:[…]
− the presence on the market in the UK [HMR regulation 73(1)] (commercial and non-commercial supply);
− countries other than the UK where the product is authorised or on the market."

II.B.6.1. Format and layout
"The Organisational Structure of the MAH, Annex B
- *The lists of contracts and agreements*

Sources of safety data, Annex C
- *Lists associated with the description of sources of safety data e.g. affiliates and third party contacts*

[…]

Pharmacovigilance System Performance, Annex F
- *Lists of performance indicators*
- *Current results of performance assessment in relation to the indicators"*

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

Finding MA.3 a)
There was no UK PSMF in place at ROVI until January 2022, despite the requirement to have a UK PSMF has been in place since 01 January 2021. The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11, Regulation 182 has been in effect since 01 January 2021 and requires that the MAH must have a UK PSMF and make this available on request of the licensing authority.
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.3 b)
A current and up-to-date UK PSMF was not provided to the MHRA when requested for preparation of the inspection. Although the UK PSMF was updated monthly, it was only finalised and approved every six months and as a result, the PSMF provided prior to inspection on 07 November 2022 (initially

requested on 28 October 2022), contained information based on the date of the last PSMF update on 30 June 2022, which was outdated at that time.

The below examples were identified in this PSMF which were out of date due to this process:

- PSMF Annex F only contained metrics up to June 2022.
- PSMF Annex H did not include the PLGB licence for the [redacted] which was authorised in the UK since July 2022.

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.3 c)

The following deficiencies were identified with the information presented in the UK PSMF [redacted] dated 30 June 2022):

i. Annex C1. [redacted] only included the UK ROVI affiliate as a site of safety information intake rather than all global main units for safety data collection.

ii. Annex H. [redacted] did not include full information regarding the authorisation or presence on the market of UK authorised products in non-UK territories. While column J, indicated whether the product was present on the market in the EU, no further information on the specific countries was included. In addition, there was no information on non-EU countries. For example:
   a. [redacted] products were sold in 12 EU countries and 26 non-EU countries such as South Africa, Israel, Brazil and Georgia.

b. [redacted] products were sold in Spain, Italy and Israel.
c. [redacted] products were sold in eleven EU countries and in eleven other non-EU countries such as Russia, Turkey and China.

Annex H also did not include information regarding presence on the UK market for UK authorised products.

iii. The service provider Atrevia was not included in PSMF Annex B. 'Organisational structure of the MAH' even though the screening of social media accounts (Twitter and LinkedIn) for AEs was outsourced to this provider since 2018.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

[redacted]

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

MA.4 Management and reporting of ADRs

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance, Regulation 188

"(1) The holder of a UK marketing authorisation […] must in relation to the product […]:

(a) submit electronically to the licensing authority a report on all serious suspected adverse reactions that occur in the United Kingdom and countries other than the United Kingdom before the end of the period of 15 days beginning on the day following the day on which the holder gained knowledge of the reaction;
(b) submit electronically to the licensing authority a report on all non-serious suspected adverse reactions that occur in the United Kingdom before the end of the period of 90 days beginning on the day following the day on which the holder gained knowledge of the reaction;
(c) establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;
(d) collect follow-up information on reports submitted under sub-paragraphs (a) or (b) and submit it electronically to the licensing authority by way of an update to the original report within the specified time period.
[…]

(4) The holder must—
(a) monitor medical literature for reports of suspected adverse reactions to the product; and
(b) report suspected adverse reactions identified under sub-paragraph (a) in accordance with paragraph (1)."

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.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 in addition to any effort to collect missing minimum criteria for reports validation (see VI.B.2. for ICSRs validation)."
.

The following findings were noted in relation to management and reporting of ADRs arising from literature:

Finding MA.4 a)

Six cases originating from literature sources that met the reportability criteria for submission to the MHRA were not reported or were incorrectly nullified.

i. Serious cases [redacted] and [redacted] reporting events of abdominal pain and haematoma, all arose from an Italian article identified on 07 April 2021 from the weekly [redacted] literature search. ROVI had taken the decision at the time to nullify these cases on the basis that no ROVI [redacted] product had been supplied

to the hospital before the time of the events (as confirmed by locally based ROVI personnel).
However, it is expected that a follow-up attempt with the author (or in this case hospital) was performed to confirm that no ROVI product had been used. As this had not been conducted, these reports remained reportable to the MHRA as the ownership of the suspected medicinal product by the MAH could not be excluded (GVP VI.C.2.2.3.2). On inspection, order and batch data was reviewed which indicated that that no ROVI product was involved but this should be confirmed by ROVI through appropriate follow-up.

ii. Serious cases [redacted] and [redacted] reporting an event of lower gastrointestinal haemorrhage were identified on 01 January 2020 from a literature article describing the results of a retrospective observational study. ROVI did not consider these cases as reportable to the MHRA on the basis that the article presented results from a post-authorisation study.
However, as this study described in the article did not have the primary aim to identify or quantify a safety hazard related to a medicinal product, the MHRA does not consider that the exception criteria in GVP VI.C.2.2.3.2 apply.
It is acknowledged that as the article referred to generic [redacted] it is likely that other MAHs for this active could have identified this article and reported to the MHRA, meaning that the impact for this finding is minimal.

iii. Serious case [redacted] reporting deep vein thrombosis, knee pain and effusion of joint was identified from a literature article and the case was originally reported to the EMA in March 2020. ROVI latterly nullified the case on June 2020 on the basis that the causal relationship between [redacted] and the events had not been clearly stated in the article, in line with in GVP Module VI.B.1.1.2.: *"If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered for literature review by the concerned marketing authorisation holder(s)".*
However for this particular case, the guidance above has been incorrectly interpreted. The article described that the patient received [redacted] first after surgery and then experienced a deep vein thrombosis, for which [redacted] and [redacted] treatment was initiated. Therefore, a temporal relationship existed between [redacted] and deep vein thrombosis, and as this was spontaneous case causality should also be implied. Additionally, as [redacted] was administered first in isolation, the argument in line with GVP Module VI.B.1.1.2 above does not apply.

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]	

C.4.3 Minor findings

MI.1 Management and reporting of ADRs

Finding MI.1 a)

Minor data entry errors were identified with a number of [redacted] cases:

i. Case [redacted] was coded with the following non-serious events within the safety database: injection site pain, underdose, exposure during pregnancy and product quality issue. However, in relation to the coded event of "product quality issue" as the source documents described a complaint regarding the bluntness of the needle, a more specific MedDRA term should have been coded of "needle dull". This case was reported to the EMA on 13 February 2020.

ii. An event in serious case [redacted] was incorrectly coded by ROVI. Follow-up information was retrieved from [redacted] on 01 April 2019 which consisted of information from a master case created by the EudraVigilance data management team where information from previously submitted cases by ROVI and another MAH were combined. The master case included the additional reaction of "chronic renal failure worsened". However, ROVI coded this reaction as a co-manifestation of the patient's already reported subcutaneous haematoma. This approach is not considered appropriate as reactions received in competent authority cases should not be amended. In addition, the coding of this reaction as a co-manifestation also meant that it would not be included in PSUR summary tabulations

iii. Serious case [redacted] reporting events of blood loss anaemia and vaginal haemorrhage, had been downloaded from EudraVigilance. However, the source field in the safety database did not list 'Health Authority' as the source type. Only the initial sources of the ICSR, study and health care professional, had been captured. This had no impact on onward reporting and the case was not re-submitted back to the EMA.

iv. Serious case [redacted] reporting an event of haemorrhage had incorrectly been included on the safety database with the source stated as "health authority" rather than the correct source which was a HCP. This was not identified during the quality control step for case processing but as this was an invalid case, there was no impact on regulatory reporting.

v. The submission date of 31 January 2018 to the EMA for case [redacted] (reporting administration site pain) was not included on the safety database, as required in the supporting [redacted] effective date 5 March 2021). Section 7 of the manual described that following ICSR distribution, some fields must be completed, which included the field "date informed" regarding submission.
However, the date of submission was accurately recorded in [redacted] effective date 22 September 2022) Appendix 9 [redacted] For information, Appendix 9 (a spreadsheet) was used to list summary information of individual cases created in [redacted] and supported compliance management of ICSR submissions. Therefore, as the submission date for this case was present in Appendix 9, there was no impact for this finding.

vi. Serious case [redacted] did not have the report type completed in the initial and latest case version. There was no impact on inclusion of this case in PSURs and signal

detection activities as cases were extracted based on the 'source' field and the 'report type' field. There was also no impact on regulatory reporting as the case was manually entered into EVWEB, and the report type had been correctly completed in the submission.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

[redacted]

Preventative Action(s)

[redacted]

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

Finding MI.1 b)

There was no procedural documentation describing the timeframes for update and maintenance of the company product dictionary (CPD).

ROVI described verbally during the inspection that the CPD would be maintained by the [redacted] administrator based on information received from Regulatory Affairs following approval after a new marketing authorisation application.

Yet an example was identified where there was a delay of two years to add Israel as a country where [redacted] was authorised to the CPD. The ROVI PV team was informed on 18 November 2020 of the approval, but the country was only added to the [redacted] library on 14 November 2022. The first adverse event case was received from Israel on 09 November 2022, and as this was a non-serious case, there was no impact on regulatory reporting to MHRA.

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 Literature searching

ROVI utilised the [redacted] database to conduct literature searching for all products. Queries were set up by ROVI within the platform to search both international and local literature sources on a routine basis.
Local UK literature searches for [redacted] were not conducted due to the fact that [redacted] reviewed [redacted] where over a thousand local UK journals were included, meaning that the probability of identifying any further local articles from the UK in a separate search was unlikely.
Deficiencies were identified with the literature search approach used for [redacted]

Finding MI.2 a)

An article reporting a serious AE in a patient who had been administered [redacted] was not identified from the weekly literature search for [redacted]

The article reported a patient who had been admitted to hospital with COVID-19 and administered [redacted] for venous thromboembolic prophylaxis (other medications had been administered as well). The patient however went on to develop a left ventricular apical thrombus a week later, resulting in an asymptomatic anterior myocardial infarction due to extensive thrombosis of the left anterior descending artery. [redacted] was discontinued and an [redacted] initiated. *Article citation:* [redacted]

Although the article was published in September 2022, the literature search did not identify this as a source of potential safety information due to the fact that within PubMed, the abstract was only visible, which did not mention [redacted] The full article (with open access) had to be viewed through a link within [redacted] which [redacted] did not view.

Root Cause Analysis

[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 MI.2 b)

The current worldwide literature search strategy for [redacted] conducted weekly did not include the brand name of the product as part of the search query; the query was focused only at the active substance level.

Although the previous search strategy prior to 03 May 2022 did include the brand name [redacted] (for the UK market), this was removed when the strategy was updated. As no separate local literature search for UK publications was carried out, this meant that the inclusion of the brand name [redacted] in the search should still be used to ensure full coverage of this market.

This is a minor finding as a search conducted by inspectors for [redacted] returned no results from articles in 2022.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MI.2 c)

[redacted] effective 30 October 2022) stated incorrect information on the presence of ROVI owned social media channels.

In section G.4. of the SOP, it stated: *"Regarding social media, ROVI does not sponsor any platform such as Twitter or youtube in which comments from patients can be included, there is not necessary to monitor."*

However, ROVI owned Twitter and LinkedIn accounts where comments were possible to be posted by the public and were potential sources of safety information, which was routinely reviewed by the service provider Atrevia, as outlined in the addendum to the contract (dated 28 October 2020) which detailed pharmacovigilance requirements.

During the inspection, the management to safety information from social media channels was not reviewed. Since this activity was not reflected in the SOP, as part of the inspection report responses ROVI must review these processes to ensure these activities were/are being conducted as required.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

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

MI.3 PSURs

Finding MI.3 a)

ROVI incorrectly listed ADRs received from competent authorities, but which had been identified by the competent authority from a solicited source, in the serious, solicited sources column in the [redacted] PSUR #5 (DLP 03 April 2021), Appendix *3b - Cumulative and interval ST of serious and non-serious adverse reactions from post-marketing data sources.*

For example, the serious ADR of 'subdural haematoma' from cases [redacted] and [redacted] were included in the solicited column, despite being a report received by ROVI from BfArM and AIFA, respectively.

This also meant that non-serious ADRs fitting the above criteria would not be included in the summary tabulations. For example the non-serious ADR of 'rectal haemorrhage' reported in cases [redacted] and [redacted](received in the interval period) were not present in the summary tabulation for PSUR #5.

As these reactions were received from a competent authority by ROVI, they should be listed in the spontaneous serious and non-serious columns in the post-marketing summary tabulations in accordance with GVP VII.B.5.6.3. "*These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) […]*".

ROVI must conduct a thorough impact assessment to determine how many ADRs from competent authority cases were not presented in the PSUR. The impact assessment must also review the extent of this deficiency to determine how many other products and other PSURs may be affected.
For the next PSUR for [redacted] (and for other product PSURs as relevant), a statement must be included for transparency to indicate what has significantly changed since the previous PSUR. The statement must make it clear to Assessors where competent authority ADRs for solicited sources are now presented as opposed to the previous PSUR(s).

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 Quality management system

Finding MI.4 a)

Examples were identified where actions taken in response to audit findings from the ROVI PV systems audit conducted 15 – 17 November 2021 were inadequate and associated CAPA implementation was incomplete.

i. [redacted] was raised due to safety variations for a product [redacted] not being implemented in a timely manner in the Spanish market. The following issues were identified with the management of this deviation and associated CAPA:
   a) ROVI did not conduct a further documented assessment of the current existing written procedures to determine if implementation timelines were clearly defined. Although ROVI included the following corrective action to address part of the deviation - *"Describe the process for safety variations communications and implementation in Rovi SOPs"* - this corrective action had not been addressed. The SOPs were not updated to include the required wording on implementation of updated product information, as already highlighted in MA.2a).
   b) There was no further assessment of whether safety variations for other products and territories were being implemented in a timely manner to determine if the issue was wider than this one incident.
   c) The preventative action was insufficient to address the root cause of the deviation and prevent its recurrence. The preventative action was *"To check that the timelines related to safety variations follow the SOP"*, which in this case was [redacted] effective from 07 November 2022). However, the only timeline reviewed was the notification from the QPPV to the regulatory affairs manager within 5 days following receipt of a final PSUSA assessment report. No other variation implementation timelines were reviewed prior to closing the preventative action to confirm that the root cause of the audit finding had been eliminated.

ii. [redacted] was raised as "*Timelines for signal detection report writing and signal validation were specified in* [redacted] *but were not monitored"* as stated in the deviation record. The following issues were identified with the implementation of CAPA for this deviation:
   a) The corrective action for [redacted] was to update Appendix 8 (the document used for tracking the signal action process) to include a due date for validating signals. Although the template for Appendix 8 in [redacted] was updated on 27 July 2022, the document used by the MAH at the time of inspection for tracking signals had not been updated to include the additional columns.
   b) The proposed CAPA did not address part of the deviation concerning monitoring the timelines of signal detection report writing, and at the time of the inspection ROVI did not have a documented process to monitor the timeliness of periodic detection report writing. It was stated that compliance of these timelines was checked by PV when reports were produced, and in cases where reports were approved after the deadline, QA would be informed by PV and a deviation would be opened. However, this was not documented in any procedural documents. A review of the periodic detection reports produced for [redacted] in the past year did not identify any late reports.

iii. [redacted] was raised due to the lack of a quality check following transcription of cases from the safety database [redacted] to the [redacted] spreadsheet 'Appendix 9' to the [redacted] effective from 04 January 2021). This was identified during the audit as one case was found to have been incorrectly transcribed into Appendix 9. However, there was no documented further assessment or impact assessment to determine whether the quality of other cases entered into Appendix 9 had been reviewed or whether downstream activities were affected by the audit finding. As Appendix 9 was used for compliance and regulatory activities the data on the spreadsheet must be accurate

iv. There was no documented impact assessment for [redacted] The deviation was raised due to a number of identified deficiencies with the literature search approach, including validation deficiencies for the software used for literature searching and the literature search not identifying a relevant article involving a case report. There was no impact assessment of the audit finding to determine whether the literature review process was more broadly affected and to fully evaluate the impact. For example, no assessment of whether literature articles had been missed from prior searches was conducted and there was no assessment of the validation status of other systems supporting PV activities.

ROVI are strongly reminded of the below requirements in GVP Module I and IV:

- GVP I.B.11. *"It is recommended that the documentation of the quality system also includes: […] records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified."*
- GVP IV.B.2.4. "*Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate."*

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)

[redacted]

Finding MI.4 b)
A key account manager (sales representative) [redacted] had not completed their PV training for a significant time period since commencing the role. The employee started as a key account manager at ROVI on [redacted] but had only partially completed the PV training until [redacted], when the training was completed. This is unacceptable due to the potential for adverse events or other safety related information being flagged to key account managers as part of their role – such personnel must be trained to appropriately handle PV relevant information in line with company procedures.
Root Cause Analysis
[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]	

MI.5 Control of educational material

Finding MI.5 a)

Access to superseded educational material for [redacted] had not been successfully version controlled once a newer version was implemented.

The educational material – a user information guide - was developed by ROVI to encourage correct administration of the product by HCPs and patients. The material was hosted on [redacted] and placed alongside a video demonstration of administration. Although the material and video were only accessible to HCPs on the website, patients could be provided with printed copies of the user guide at the request of HCPs.

The current version of the material on the website was [redacted] However through a basic Google search for [redacted] the second search result returned a superseded version [redacted] The only difference between the versions was reference to the educational video and how to access further information on the product, which was not present in version [redacted] Although the impact is minimal, ROVI should ensure there are sufficient procedures in place to prevent superseded product material being publicly available. This would be of particular importance if any wording on safety or administration guidance of the product had changed.

[redacted]

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]	

C.4.4 Comments

1. Rovi must ensure that updates to product information that are included as part of a DCP renewal procedure and include safety warnings or safety information, are provided to the

MHRA for expedited renewal so that UK mock-ups of product information can be prioritised for review and approval.
For example, the UK SmPC and PIL for [redacted] required updating following the PSUR assessment report [redacted] for the [redacted] PSUR covering the period 04 April 2020 to 03 April 2021. The addition of a new safety warning regarding acute generalised exanthematous pustulosis (AGEP) with [redacted] was recommended. The MAH received RMS approval for the updates as part of a renewal procedure on 31 March 2022 but at the time of the inspection, MHRA approval for the UK SmPC and PIL mock-ups was still outstanding. As the update included safety information the MAH should have requested an expedited review by the MHRA to avoid any undue delays in updating product information.

2. Rovi had submitted a type IB variation to the MHRA on 11 August 2022 to align with the [redacted] reference medicinal product. As the variation was to extend the therapeutic indication to that of the reference medicinal product, this should have been submitted as a type II complex variation rather than a type IB variation. ROVI should withdraw the present variation and resubmit it as a type II. As the UK are CMS to this MRP, ROVI should inform the RMS regarding the resubmission as a type II variation.

3. The educational material – the user information guide – for [redacted] was briefly reviewed by the MHRA Advertising unit. The following points were noted:
    - It recommended that the material should point to the PIL more clearly and prominently as company product information for patients should not attempt to undermine the PIL.
    - The SmPC for [redacted] suggests that for some indications, administration should be when the patient is lying down, but the materials do not depict this, only that the patient should be in a comfortable position. Please consider addressing this discrepancy.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

The Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- 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.
- 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	Insert inspection number tbc	**DATES**	12 – 15 December 2022
PHARMACOVIGILANCE INSPECTION OF	Laboratorios Farmacéuticos ROVI	**START TIME**	09:00 GMT
LOCATION	Remote Insert inspection address	**INSPECTION TEAM**	[redacted] (lead inspector), [redacted] (observer from the TGA)

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

- Collection and collation of sources of safety data
- Management and reporting of ADRs
- Signal management

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, 12 December 2022 (Day 1)	
Opening Meeting **09:00 GMT**, 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 ROVI (~20 mins) with an overview of the company and pharmacovigilance system. The presentation should focus on the topics listed for	Opening meeting attendees: • [redacted] – EU-QPPV/UK-QPPV • [redacted] Clinical Pharmacology Manager (EU-QPPV/UK-QPPV deputy) • [redacted] – Country Manager UK & National contact person for Pharmacovigilance in UK • [redacted] – Medical Director

inspection and any relevant ongoing remediation work in the pharmacovigilance system. Please also highlight any significant recent or upcoming changes to the pharmacovigilance system.	• [redacted] Senior Pharmacovigilance Technician • [redacted]- Senior Pharmacovigilance Technician • [redacted] - Senior Pharmacovigilance Technician • [redacted] Pharmacovigilance Technician • [redacted] - Pharmacovigilance Technician • [redacted] - Pharmacovigilance Technician • [redacted] - Pharmacovigilance Trainee • [redacted] - Pharmacovigilance Trainee • [redacted] - Quality assurance GCP/GVP Technician • [redacted] - Medical Automation Quality Assurance Technician • [redacted] – Quality Director • [redacted] – Regulatory Affairs Manager • [redacted] - Head of R&D - QA
Session 1 - Management and reporting of ADRs ***Provisionally 10:00 GMT*** Including but not limited to: • Case processing and assessments • Follow-up activities • Expedited reporting of ICSRs • Case quality in the safety database, submission to MHRA	MHRA attendees: [redacted] Interviewee(s): Availability from 8:00 GMT to 17:00 GMT (lunch time: 12:30 GMT to 13:00 GMT) • [redacted] – EU-QPPV/UK-QPPV • [redacted] – Clinical Pharmacology Manager (EU-QPPV/UK-QPPV deputy) • [redacted] – Country Manager UK & National contact person for Pharmacovigilance in UK • [redacted] – Senior Pharmacovigilance Technician • [redacted]- Senior Pharmacovigilance Technician • [redacted] Senior Pharmacovigilance Technician

	• [redacted] - Quality assurance GCP/GVP Technician
Tuesday, 13 December 2022 (Day 2)	
Session 2 - Signal management ***Provisionally 08:30 GMT*** 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 by the company to provide an overview of signal management activities.	MHRA attendees: [redacted] Interviewee(s): Availability from 8:00 GMT to 17:00 GMT (lunch time: 12:30 GMT to 13:00 GMT) • [redacted] EU-QPPV/UK-QPPV • [redacted] – Clinical Pharmacology Manager (EU-QPPV/UK-QPPV deputy) • [redacted] – Senior Pharmacovigilance Technician • [redacted] - Senior Pharmacovigilance Technician • [redacted] - Senior Pharmacovigilance Technician • [redacted] - Pharmacovigilance Technician • [redacted] - Quality assurance GCP/GVP Technician
Session 3 - Sources of safety information ***Provisionally 10:30 GMT*** Including but not limited to: • Medical information in the UK • Product quality complaints in the UK • Management of contracts and agreements (PVAs/SDEAs) • Literature searching	MHRA attendees: [redacted] Interviewee(s): Availability from 8:00 GMT to 17:00 GMT (lunch time: 12:30 GMT to 13:00 GMT) • [redacted] – Country Manager UK & National contact person for Pharmacovigilance in UK • [redacted] – Medical Lead UK • [redacted] - Quality Director • [redacted] – EU-QPPV/UK-QPPV • [redacted] – Clinical Pharmacology Manager (EU-QPPV/UK-QPPV deputy) • [redacted] – Senior Pharmacovigilance Technician

	• [redacted] Senior Pharmacovigilance Technician • [redacted] Senior Pharmacovigilance Technician • [redacted] - Pharmacovigilance Technician • [redacted] - Quality assurance GCP/GVP Technician • [redacted] - Pharmacovigilance Technician

Wednesday - Thursday, 14 – 15 December 2022 (Days 3 - 4)

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

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 title of the designated contact point.
Designated contact point:

- [redacted] – EU-QPPV/UK-QPPV
- [redacted] – Clinical Pharmacology Manager (EU-QPPV/UK-QPPV deputy)
- [redacted] - Quality assurance GCP/GVP Technician
- [redacted] – Country Manager UK & National contact person for Pharmacovigilance in UK

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