Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Seqirus

MHRA Inspection Number: Insp GPvP 47991/16642630-0003

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ABBREVIATIONS

CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
DLP	Data Lock Point
EMA	European Medicines Agency
EPSS	Enhanced Passive Safety Surveillance
EU	European Union
GVP	Good Vigilance Practice
HLT	High Level Term
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NAP	Nationally Authorised Product
PBRER	Periodic Benefit Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QA	Quality Assurance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Seqirus [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted] SCRATCH Pharmacovigilance GmbH & Co. KG Schlossstr. 25 35510 Butzbach Germany [redacted]
Date(s) of inspection:	07 – 11 September 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
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:	Processes relating to ICSR management, data extraction from the safety database and signal management were examined for [redacted]
Name and location of EU QPPV:	[redacted] Address and contact details as above.
Global PV database (in use at the time of the inspection):	Argus, [redacted] (commercially available)
Key service provider(s):	ICSR management activities provided by PrimeVigilance. Safety database hosted and maintained by IQVIA Inc. (previously Foresight Group) Signal detection support provided by Commonwealth Informatics Inc.
Inspection finding summary:	03 Major findings 01 Minor finding
Date of first issue of report to MAH:	15 October 2020, amended on 30 October 2020 to add clarification to post-inspection request 2 for finding MA.3 a)
Deadline for submission of responses by MAH:	Initial: 19 November 2020 Follow-up: 22 January 2021
Date(s) of receipt of responses from MAH:	Initial: 19 November 2020 Follow-up: 18 January 2021
Date of final version of report:	29 January 2021
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Insert Company Name was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable EU and UK pharmacovigilance regulations and guidelines. In particular, reference was made to Regulation 726/2004/EC as amended, Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules.

A list of reference texts is provided at Appendix I.

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Seqirus is the vaccines division of CSL Ltd. and was established in 2015 following CSL's acquisition of the [redacted] business and its subsequent integration with [redacted] The pharmacovigilance system covers pandemic, pre-pandemic and seasonal influenza vaccines authorised as NAPs or CAPs in the EU by the following MAHs:

- Seqirus UK Ltd.
- Seqirus Vaccines Ltd.
- Seqirus S.r.l.
- Seqirus GmbH
- Seqirus Netherlands B.V.

The inspection focussed on two seasonal vaccines authorised and marketed in the UK, the NAP [redacted] (surface antigen, inactivated, adjuvanted, PL [redacted] and its unbranded duplicate licence [redacted] and the CAP [redacted] (surface antigen, inactivated, prepared in cell cultures, [redacted]

Seqirus' Pharmacovigilance & Risk Management (PVRM) department is responsible for the overall safety evaluation of the Seqirus influenza vaccines. Key personnel are based in the UK, the Netherlands and Australia. Specific PVRM responsibilities include the production of PSURs, signal detection and analysis, and RMP management. The role of the EU QPPV is subcontracted to SCRATCH Pharmacovigilance GmbH.

ICSR management activities from data entry to regulatory submission are outsourced to PrimeVigilance; however, PVRM physicians may be involved in the assessment of cases. The global safety database, Argus, is hosted and maintained by IQVIA (formerly Foresight Group). In addition, Commonwealth Informatics Inc. provide support for signal detection in relation to the statistical analysis of database extracts.

At the time of the inspection, the PSMF was located in Germany, therefore Paul-Ehrlich-Institut (PEI) was the Supervisory Authority.

B.2 Scope of the inspection

The inspection focussed on a review of the systems and processes relating to the management of ICSRs, extraction of data from the safety database for the purposes of critical pharmacovigilance activities and signal management activities. The inspection was performed remotely on 07 – 11 September 2020. The inspection was predominantly conducted via

document review; however, personnel involved in pharmacovigilance and quality assurance were available via teleconference throughout the inspection for scheduled and ad-hoc calls.

The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

The collection and collation of safety information from spontaneous and solicited sources, maintenance of the reference safety information 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 pharmacovigilance inspection.

B.3 Documents submitted prior to the inspection

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The company submitted a PSMF [redacted] release date 30 July 2020) to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection. The detail of these request is contained within document request sheet A.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. A closing meeting to review the inspection findings was held remotely on 11 September 2020.

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

SECTION C: INSPECTION FINDINGS

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

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 which are graded as critical or major will be shared with the EMA, other EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

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

C.4.2 Major findings

MA.1 Signal Management

Requirements:

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.8. Facilities and equipment for pharmacovigilance
"*Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.*"

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.2. Validation of reports
"*Reports, for which the minimum information is incomplete, should be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.*"

GVP Module IX – Signal management (Rev 1)
IX.B.2. Signal detection
"*Data from all appropriate sources should be considered […].*"

IX.B.5. Quality requirements
"*Any signal management system should be clearly documented to ensure that the system functions properly and effectively, […] that there are provisions for appropriate control and, when needed, improvement of the system.*"

"*The organisational roles and responsibilities for the activities including maintenance of documentation, quality control and review, and for ensuring corrective and preventive action should be assigned and recorded.*"

"*The performance of the system should be controlled […].*"

"*Documentation demonstrating compliance with these requirements should be available at any time, including justification / evidence for the steps taken and decisions made.*"

MAHs are obliged to ensure that information on the benefits and risks of their products is evaluated on an ongoing basis and appropriate action is taken in response to new information that impacts on the benefit-risk balance.

In addition to routine signal detection activities, Seqirus also implemented Enhanced Passive Safety Surveillance (EPSS) for its seasonal influenza vaccines in accordance with the EMA *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU* (EMA/PRAC/222346/2014, dated 10 April 2014) at the beginning of the northern hemisphere influenza season with the aim of rapidly detecting a clinically significant changed in the frequency and/or severity of expected adverse reactions or adverse events of interest (AEIs).

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The following findings were noted in relation to signal management:

Finding MA.1 a)
Seqirus had not considered invalid cases in the safety database as a source of safety information in signal detection activities until April 2020, when the requirement for a quarterly review of these was added to [redacted] *Signal Management Process*

(date effective 08 April 2020).

In addition, only a limited retrospective review of invalid cases received since April 2017 was conducted to establish whether they yielded any relevant safety information that might impact on the benefit-risk profile of Seqirus' products. At the beginning of June 2020, Seqirus retrospectively reviewed the invalid cases received in the first quarter of 2020 to understand the frequency and nature of invalid cases; however, the outcome and conclusions of this review, including their rationale were not documented.

Root Cause Analysis

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

Finding MA.1 b)

There were insufficient provisions for the quality control of signal management activities:

i. Seqirus did not have any evidence that appropriate checks or validation of the search parameters used for the extraction of data from the safety database for use in the statistical disproportionality analysis were performed to ensure that these retrieved complete and accurate data. As a mitigating factor, the review of signal detection inputs and outputs during the inspection did not indicate that any cases were missing in the extracted data for signal detection.

ii. There was insufficient documentation of the justifications supporting the decisions made during the qualitative review of drug-event-combinations (DEC) flagged as signals of disproportionate reporting. As an example, the statistical analysis report for June 2019 highlighted the events of "head injury" and "impaired work ability" with [redacted] but the associated tracker did not provide any further justification apart from "This is a new SDR, No signal identified".

iii. There had been no documented control process of the signal detection activities since June 2019 to ensure that these functioned properly and effectively. Prior to this, the relevant Therapeutic Area Safety Head reviewed and co-signed all signal detection reports; however, this requirement was removed with the update of [redacted] *Signal Management Process* from [redacted] date effective 08 July 2019).

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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Deliverable(s)	Due Date(s)

Preventative Action(s)

Deliverable(s)	Due Date(s)

Finding MA.1 c)

Minor discrepancies were identified in the reporting of the [redacted] (EPSS) activities and associated procedural documentation:

i. The [redacted] EPSS 2019 final report, submitted to competent authorities in Appendix 8 of the [redacted] 15 March 2020), incorrectly included two ineligible adverse reactions in the analysis of safety data. *Table 3: rAEI reporting rate (%) fo[redacted] (total and per age group) from 04-Nov-2019 to 28-Nov-2019* included the serious event of "pyrexia" (reported from case [redacted] and non-serious event of "local reaction" (reported from case [redacted]); however, the reactions were not eligible for inclusion as neither the vaccination date nor the vaccination card number were reported with these cases.

Enhanced Passive Safety Surveillance of Seqirus Seasonal Trivalent and Quadrivalent Influenza Vaccines [redacted] dated 12 August 2019), [redacted] defined eligible exposure as "exposure data with at least information on the brand, an available vaccination date and a valid vaccination card number. In addition, [redacted] stated "For the purpose of the EPSS, an "Eligible adverse event report" is defined as a valid ICSR which contains a unique vaccination card number of the EPSS. Additionally, it should correspond to eligible exposure data."

ii. The [redacted] EPSS 2018 final report, submitted to competent authorities in Appendix 2 of the [redacted] 2019 PSUR [redacted] DLP 15 March 2019), incorrectly included a case of asthenia (received for 201806038) in the counts for the reactogenic adverse event of interest (rAEI) of malaise in Table *3 Frequency and reporting rate (percentage) for*

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Reactogenic Adverse Events of Interest (rAEIs) [redacted]® *(in total and per age group) per seriousness, between 05 Nov 2018 to 04 Dec 2018.*

As per Appendix 1 *Preferred Terms (PTs) linked to the rAEIs* of the annual EPSS plans, Seqirus included adverse reactions coded to the MedDRA PT "asthenia" in the counts for the rAEI of "malaise" received during the EPSS period due to the same medical concept. While asthenia and malaise do come under the same MedDRA HLT (Asthenic conditions), both events are separate PTs. As such, asthenia, as an unsolicited ADR term, should have been presented separately in the final EPSS report in accordance with the EMA *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*, section 3.2. d. *Expedited summary safety report section "Safety data"*.

iii. The 2019 plan for *Enhanced Passive Safety Surveillance of Seqirus Seasonal Trivalent and Quadrivalent Influenza Vaccines* [redacted] dated 12 August 2019), Appendix 2 *RMP Risks, per Product* did not include "haemolytic disorders" as an important potential risk for [redacted] even though this was listed in the [redacted], date of final sign off 29 September 2017) as an important identified risk.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

MA.2 Quality Management System

Requirements:

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.6. Responsibilities for the quality system within an organisation
"*For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for: […]*

- *identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary; […].*"

GVP Module IV – Pharmacovigilance audits (Rev 1)
IV.B.2.3.2. Reporting
"*The findings of the auditors should be documented in an audit report and should be communicated to management in a timely manner.*"

IV.B.2.4. Actions based on audit outcomes and follow-up of audits
"*The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.*" [emphasis added]

The following findings were noted in relation to the quality management system:

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Finding MA.2 a)
There were delays of up to eight months in issuing the initial and finalised audit reports after the audit of [redacted] was conducted on 02 – 03 October 2018 and during which two critical findings and several major findings were identified. The initial audit report was issued over six weeks late on 17 December 2018 and the finalised audit report was not issued until 24 September 2019 with a delay of approximately eight months. The SOP in place at the time, [redacted] *Audit Management* (effective from 30 May 2017 to 07 March 2019, now superseded by [redacted] *R&D QA Audit Management*) stated that initial audit reports must be issued within 28 calendar days following the last day of the audit, and final audit reports must be issued within 42 calendar days of issuance of the initial audit report. The current version of [redacted], date effective 25 October 2019) included the same timeline for the initial audit plan and stipulated that Final CAPA Plans must be issued within 42 calendar days of issuance of the initial audit report.
Root Cause Analysis
[redacted]

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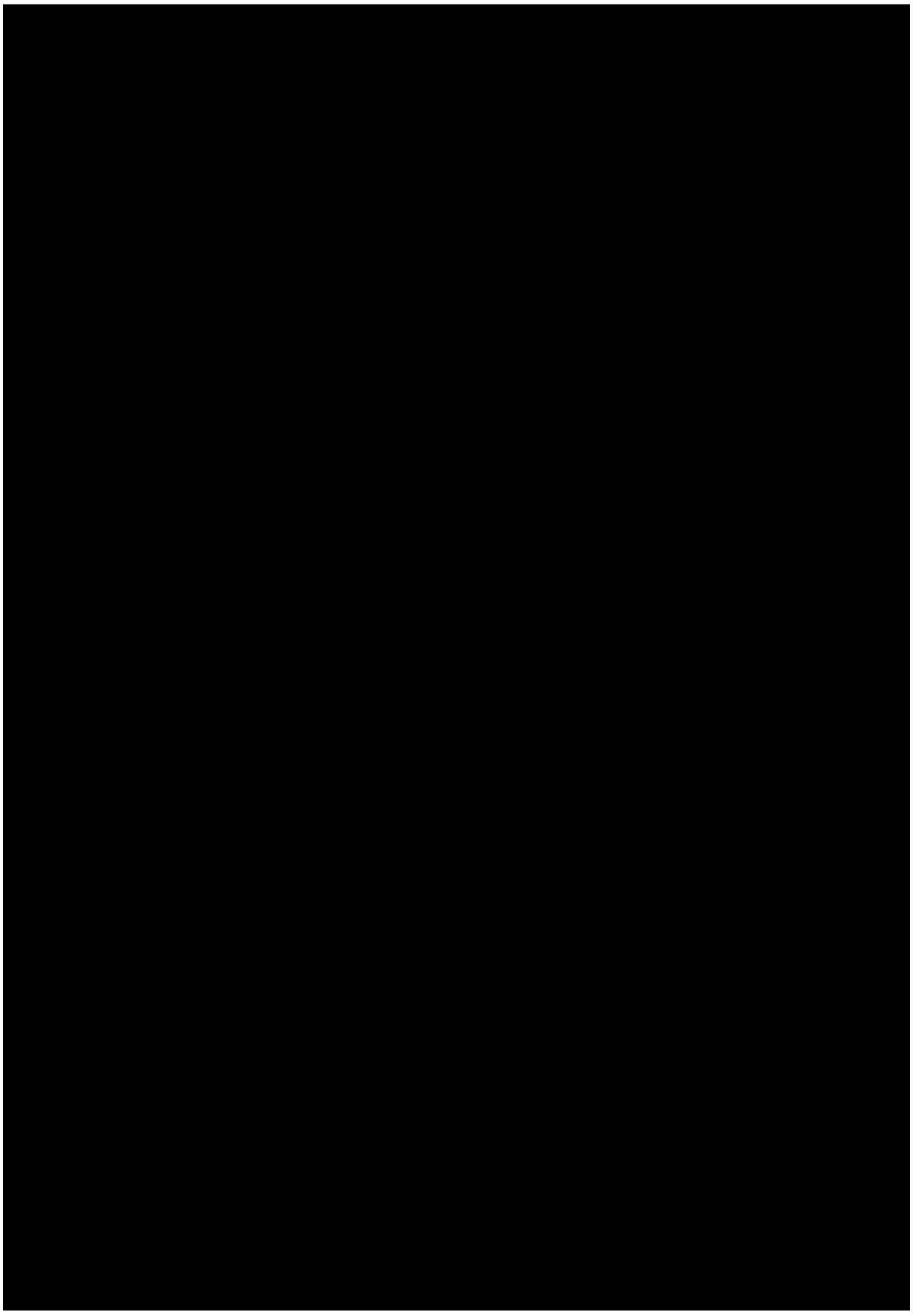

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.2 b)

Examples of CAPA from audits and deviations were identified for which no meaningful risk assessment had taken place after the original CAPA due date had passed or was extended to establish whether any further actions were required to mitigate the impact of the identified non-compliances in the meantime.

i. The following CAPA were proposed to address critical and major findings identified from the audit of [redacted] on 02 – 03 October 2018:

- [redacted] related to a critical finding for a deficiency of the CAPA portion of Foresight's quality system. The initial CAPA implementation due date on 09 December 2019 was not met and was extended to 31 December 2020 on 12 December 2019.

- [redacted] related to a major finding for the incorrect mapping of the medically confirmed field from both source safety databases into the new safety database during the data migration that was completed in April 2017. The initial CAPA implementation due date of 30 March 2020 was extended to 30 November 2020 on 12 December 2019.

For both CAPA, the risk assessment completed on 12 December 2019 only stated "Delay in submission of CAPA information from vendor". More detailed risk assessments that fully investigated whether any further actions were required to mitigate the impact of the findings in the interim were not completed until 02 September 2020 after the CAPA records were requested by inspectors as part of the pre-inspection document requests sent on 20 August 2020.

As per [redacted] *R&D QA Audit CAPA Management* [redacted] date effective 25 October 2019), [redacted] all overdue CAPA needed a risk assessment to be conducted in order to identify whether any further actions were required in order to mitigate the interim risk until the CAPA was implemented.

ii. Deviation [redacted] was initiated on 14 August 2019 after line listings were not created and made available for signal detection purposes. The due date of the associated four CAPA was 18 March 2020 but they were not completed until 14 May, 19 May and 28 July 2020. The extension to the CAPA due dates was only documented in the TrackWise record when the respective CAPA was closed. In addition, only a limited risk assessment was conducted to establish the impact of the delayed CAPA completion and whether any mitigating actions were required in the meantime.

Procedure [redacted] *Deviation and CAPA Management* [redacted] date

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effective 30 October 2019), [redacted] stated "If a CAPA cannot be completed by its due date then the CAPA is overdue. All overdue CAPAs require a risk assessment to determine whether further mitigation actions are needed to manage the interim risk whilst the CAPA is being implemented. […] The risk assessment must be approved by QA and should be recorded or attached into the record."

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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[redacted]

MA.3 Management and Reporting of Adverse Reactions

Requirements:

Directive 2001/83/EC as amended, Article 107(3)
"*Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the 'Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.*"

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.4. Data management
"*Data received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided during data entry or electronic submission.*"

VI.B.5. Quality management
"*[…] marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as […] data coding […].*"

VI.C.4. Submission modalities of ICSRs in EU
"*a. Serious ICSRs*
- The marketing authorisation holder shall submit all serious ICSRs that occur within or outside the EU, including those received from competent authorities outside the EU, to the EudraVigilance database only."

The following finding was noted in relation to management and reporting of adverse reactions:

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Finding MA.3 a)

Examples of ICSRs were identified where Seqirus had coded non-specific diagnoses, such as hypersensitivity, as the only adverse event Preferred Term (PT), while the more specific terms describing the reaction had only been coded as symptoms in Argus. Terms coded as symptoms were not included in the PSUR summary tabulations:

- [redacted] was a serious report received from the USA for [redacted] reported to EudraVigilance on 19 April 2019. The event PT 'hypersensitivity' was coded; however, the source documentation stated, "*Pt reported to Health Center Provider and HCM/RN that she had an allergic reaction 3-4 hours after receiving Hepatitis A and Influenza vaccinations […]. She states that she was lightheaded for a little while, her uvula swelled to 3 times its normal size, had severe body aches and some nasal congestion*". The terms enlarged uvula, dizziness, nasal congestion, and pain were coded in Argus as symptoms.

- Regulatory authority case [redacted] was a serious report received from the USA for [redacted]. The event PT 'hypersensitivity' was coded; however, the source documentation stated, "*My daughter experienced an allergic reaction to the flu shot […] She had hives all over her left arm; her left arm was red, swollen, and hot to the touch; her left leg was red and hot to the touch; and most significantly, her throat was tight."* The terms peripheral swelling, erythema, skin warm, throat tightness, and urticaria were coded in Argus as symptoms.

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- Regulatory authority case [redacted] was a serious report received from the USA for [redacted]. The event PTs, 'Autoimmune disorder' and 'Vaccine complication' had been coded; however, the source documentation stated, "*Received influenza 4 strain [redacted] shot […] Within 7 days, left knee began aching continuously as well as both shoulder joints and rotator cuff popping. Orthopedic doctor took xrays stating knee required a full replacement and to temporarily relieve the pain administered a cortisone shot to the knee. Pain subsided in knee for 20 days, however the shoulder joints kept getting worse then all my joints in the body became inflamed. Dr ordered multiple blood tests to isolate issue, results indicated an auto immune disease however it is not Rheumatoid Arthritis, not Lupus, not Scleroderma but Sedimentary Rate was very high out of range […] Dr has diagnosed, symptom is vaccine induced arthropathy*". The terms red blood cell sedimentation rate increased, arthropathy, arthritis, and arthralgia were coded in Argus as symptoms.

PrimeVigilance [redacted] 4 *Coding Conventions* ([redacted] date effective 31 March 2019), [redacted] stated "If a definitive diagnosis and its characteristic signs or symptoms are reported, select a term for the diagnosis only. Exceptions to this rule are diagnoses that can present with a wide variety of symptoms, such as hypersensitivity (see terms related to unspecific diagnoses below) and withdrawal reactions (see [redacted] and [redacted]

Post-inspection request 1: Seqirus should address in their responses how the terms currently coded as symptoms only would appear in the statistical signal detection reports as well as in the structured fields in ICSRs submitted to EudraVigilance.

Post-inspection request 2: It is expected that Seqirus shares the details of this finding with PrimeVigilance and liaises with this service provider to produce consolidated responses to address the identified non-compliance.

In addition, and separately to the responses to the inspection report, MHRA requests that PrimeVigilance performs a documented impact assessment in relation to this finding to determine the extent and impact across the client base of PrimeVigilance. This assessment should consider all marketing authorisation holders with a UK authorised product. Corrective and preventative actions should be described, where applicable, as well as deliverables and due dates. The methods used for the impact assessment should also be outlined.

The MHRA requests that the documented impact assessment by PrimeVigilance is submitted directly to the Lead Inspector at [redacted] for receipt by 19 November 2020.*

Clarification added by lead inspector on 30 October 2020: *If Seqirus identify in the further assessment that that none of the affected cases (including but not limited to those listed in the finding) were processed by PrimeVigilance, then the separate impact assessment by PrimeVigilance is not required.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

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[redacted]

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

Finding MA.3 b)

Two serious cases received for [redacted] from the US via the Vaccine Adverse Event Reporting System (VAERS) had not been reported to EudraVigilance (also refer to finding MA.3 a):

- [redacted] was received on 14 March 2018 and reported the events arthralgia, arthritis, arthropathy, autoimmune disorder, blood test abnormal, red blood cell sedimentation rate increased, vaccination complication and x-ray limb abnormal.
- [redacted] was received on 16 August 2018 and reported the events erythema, hypersensitivity, peripheral swelling, skin warm, throat tightness and urticaria.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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

C.4.3 Minor findings

MI.1 Periodic Safety Update Reports

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Finding MI.1 a)
The same MedDRA event PT was presented under multiple SOCs in the *Cumulative and Interval Summary Tabulation of Serious and Non-serious Adverse Reactions from Post-marketing Data Sources* for the [redacted] PSUR (No. 2, dated 18 May 2020) and [redacted] PSUR ([redacted] dated 15 May 2020). For example, in the [redacted] PSUR, the event PT 'Mouth swelling' was presented under the 'Immune system disorders' SOC, the 'Gastrointestinal disorders' SOC and the 'Skin and subcutaneous tissue disorders' SOC. This impacted 14 PTs for 17 reported events in the [redacted] PSUR, and 9 PTs for 11 reported events in the [redacted] PSUR. The event counts were not duplicated and hence there was no impact on the total event counts. During the inspection, Seqirus stated that the root cause was most likely associated with coding the affected events to non-primary SOCs, and that during the MedDRA version upgrade (implemented on 02 May 2020), impacted events were automatically recoded to the primary SOC. However, in the listing of all adverse event reports provided for the purposes of the inspection (A2), the relevant events were still coded to the non-primary SOC.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)

Section 43

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MI.1 b)

Section 5.2.1 *Post-Authorisation (Non-Clinical Trial) Exposure* of the [redacted] PSUR [redacted] dated 15 May 2020) included incorrect sales data for Australia.

For the period of 16 March 2019 to 15 March 2020, sales data for Australia was presented as 5,908,760 doses sold. However, Seqirus confirmed during the inspection that the actual volume sold during this period was 1,700,330. This represented a difference of 4,208,430 doses, which was approximately 13.5% of the total exposure (31,046,718). The number of doses sold was used as a direct estimation of patient exposure.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

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

C.4.4 Comment

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1. At the time of the inspection, two different versions of the [redacted] had been provided to MHRA for the two UK product licences of the same influenza vaccine. For the branded licence [redacted], the RMP held by the MHRA was [redacted] (dated 16 January 2017); however, the RMP submitted for the unbranded duplicate licence [redacted] was [redacted] (dated 29 September 2017). Even though the change between the two RMP versions was not significant, it is recommended that Seqirus ensures that the same RMP version is provided to MHRA for all product licences covered.

[redacted]

2. SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

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

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D “Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	**Insp GPvP 47991/16642630-0003**	**INSPECTION TEAM**	Sophie Radicke (lead inspector) Elizabeth Webb
PHARMACOVIGILANCE INSPECTION OF	Seqirus	**DATES**	07 - 11 September 2020

N.B. the inspection plan may be subject to change in the lead-up to, or during, the inspection

- An opening meeting, led by the lead inspector, will be held by video conference at 8 am (BST) on Monday, 07th September 2020. The agenda will be:
  - Review of the scope and arrangements for the inspection
  - Seqirus are asked to lead a short company presentation (max. 20 mins) which aims to provide the inspectors 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.
- A specific time will be agreed for an overview via video conference of each topic (max. 20 mins) to be covered on day 2 of the inspection. The following timings are envisaged:
  - Data management I, Data management II and Ongoing safety evaluation: 8 – 10.30 am (BST), to include a comfort break if required
- The remainder of the inspection will consist of remote document review, written requests and ad hoc video/telephone clarifications with subject matter experts as required, at a pre-agreed time based on SME availability.
- Feedback on any non-compliance *was* provided during the closing meeting video conference *at 9* am (BST) on Friday, 11th September *taking* into consideration the distribution of staff across different time zones. All relevant personnel are welcome to attend the closing meeting.

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The inspection will be focused on a review of the specific pharmacovigilance activities listed below for Fluad, Adjuvanted Trivalent Influenza Vaccine and Flucelvax Tetra

Topics for review	Personnel (Name & job title)
Topic 1 – Data management I • Case quality in the safety database • Oversight of service providers	• [redacted]

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	• [redacted]
Topic 2 – Data management II • Extraction of data from the safety database for the purposes of critical pharmacovigilance activities including PSURs and signal management	• [redacted]
Topic 3 – Ongoing safety evaluation • Signal detection and management activities • Signal tracking • Enhanced Passive Safety Surveillance	• [redacted]

Seqirus should complete the below with the names and job titles of the designated contact point and those staff who will be joining the opening meeting.

Designated contact point during the inspection:

[redacted]

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