Medicines & Healthcare products Regulatory Agency

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Alnylam Netherlands B.V.

MHRA Inspection Number: Insp GPvP 50597/30734220-0001

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ABBREVIATIONS

AASL	Alnylam Always Serious List
ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CMVO	Case Management and Vendor Oversight
CSR	Clinical Study Report
DAEN	Database of Adverse Event Notifications
DLP	Data Lock Point
EMA	European Medicines Agency
ETL	Expected Term List
EU	European Union
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
GPSRM	Global Patient Safety & Risk Management
GSD	Global Safety Database
GSS	Global Safety Systems
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IIS	Investigator-initiated Study
IME	Important Medical Event Terms
KPI	Key Performance Indicator
LSO	Local Safety Officer
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MSRM	Medical Safety & Risk Management
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

PSMF	Pharmacovigilance System Master File
PSP	Patient Support Programme
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOP	Standard Operating Procedure
SRMT	Safety Risk Management Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
TQ	Targeted Questionnaire
UK	United Kingdom
VAERS	Vaccine Adverse Event Reporting System

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection
System(s) inspected:	Alnylam Netherlands B.V. [redacted]
Site(s) of inspection:	Alnylam Pharmaceuticals, Braywick Gate, Braywick Road, Maidenhead, Berkshire SL6 1DA.
Main site contact:	[redacted] – Director, PV QA Alnylam Pharmaceuticals Braywick Gate, Braywick Road Maidenhead SL6 1DA United Kingdom [redacted] Work: [redacted] Mobile: [redacted]
Date(s) of inspection:	10 – 13 July 2023 Day 1 (10 July 2023): remote. Days 2 – 4 (11 – 13 July 2023): onsite.
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted] Claire Longman, [redacted]
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:	As part of the general systems review, data from all UK authorised products were reviewed and included: [redacted] Signal management review focused on [redacted] and [redacted].
Name and location of UK QPPV:	[redacted] MD, MBA PrimeVigilance s.r.o. Vaclavske namesti 2132/47, Prague 110 00, Czech Republic Fax : [redacted] Mobile : [redacted] Email : [redacted]
Global PV database (in use at the time of the inspection):	[redacted] (commercially available)
Key service provider(s):	EU/UK QPPV, global/local literature search, local safety officer (LSO) and regulatory intelligence services provided by PrimeVigilance. Medical information services provided by PPD. Safety case processing services provided by Syneos Health.
Inspection finding summary:	0 Critical finding(s) 2 Major finding(s) 5 Minor finding(s)
Date of first issue of report to MAH:	04 September 2023
Deadline for submission of responses by MAH:	09 October 2023 Follow-up 1: 20 December 2023

Date(s) of receipt of responses from MAH:	09 October 2023 Follow-up 1: 12 December 2023
Date of final version of report:	19 January 2024
Report author:	[redacted] Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Alnylam Netherlands B.V. (Alnylam) 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.

Alnylam Pharmaceuticals is a biopharmaceutical company focused on the discovery, development and commercialization of RNA interference (RNAi) therapeutics. The company, founded in 2002, is headquartered in Cambridge, Massachusetts. Alnylam Netherlands B.V. is a subsidiary of Alnylam Pharmaceuticals and is the marketing authorisation holder for all products in the UK. At the time of the inspection, Alnylam Netherlands B.V. held a national GB licence and a central EU licence in respect of Northern Ireland for each of the following products:

- [redacted] ▼ ([redacted]), indicated for
- [redacted] ▼ ([redacted]), indicated for [redacted]
- [redacted] ▼ ([redacted]), indicated for [redacted]
- [redacted] ▼ ([redacted]), indicated for

PV activities were managed by a combination of local and global teams. Alnylam's Global Patient Safety & Risk Management (GPSRM) group was predominantly located in the USA and was responsible for conducting and/or overseeing PV activities globally. Service provider Syneos Health provided case processing services since taking this over from PrimeVigilance on 25 July 2022. PrimeVigilance provided the EU/UK QPPV, local safety officers, literature search and regulatory intelligence services. Additional key PV vendors included PPD Development, L.P., for centralised call centres for adverse event and other safety information report intake.

Planned changes to the PV system included an end-to-end signal implementation project for improved tracking of safety signals, due to complete in Q3 2023, and a process review of the end-to-end reference safety information (RSI) process, due to complete in November 2023.

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems and was performed at Alnylam's offices in Maidenhead. The UK QPPV was available on site and personnel from headquarters participated in the inspection via videoconference.

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

Periodic safety update reports (PSURs), the quality management system, update and maintenance of the product information and additional risk minimisation measures 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

The company submitted a PSMF (version [redacted], effective date 30 April 2023) to assist with inspection planning and preparation. Risk management plans (RMPs), product sales data, PrimeVigilance contracts and agreements and sources of safety data were also requested by the inspection team and provided by the company prior to the inspection.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. The inspection included a remote inspection day on 10 July 2023 and three onsite inspections days.

A closing meeting was held to review the inspection findings at Alnylam Pharmaceuticals, Maidenhead, Berkshire on 13 July 2023.

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 Management and reporting of adverse reactions

Requirements:

Regulation (EC) No. 726/2004 as amended, Article 24(1)

Commission Implementing Regulation (EU) No. 520/2012, Chapter V, Article 28(1)

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance
Regulation 187 – Recording obligations on holders (1)
Regulation 188 – Reporting obligations on holders (1 and 1A)
Schedule 12A, Part 6
Content of the individual case safety report
20.—(2) 'In the case of expedited reporting, the individual case safety report must include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and any medicinal product concerned.'

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.1.2. Solicited reports
'With regard to the submission as ICSRs, solicited reports should be classified as study reports. They should have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria (see VI.B.2. for ICSRs validation).'

VI.B.2. Validation of reports
'Only valid ICSRs qualify for submission.'

'Four minimum criteria are required for ICSRs validation:
[…]
*'**b. one single identifiable patient**, characterised by at least one of the following qualifying descriptors: initials, medical record number (from general practitioner, specialist, hospital, or investigation), date of birth, age, age group, gestation period, or gender.*
[…]
*'**d. one or more suspected adverse reaction** […] the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance a marketing authorisation holder is made aware that a patient was hospitalised or died, without any further information.'*

VI.B.3. Follow-up of reports
'When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy (see VI.B.6.1. for guidance on the management of pregnancy reports), cases notifying the death of a patient, or cases reporting new risks or changes in the known risks.'

VI.B.6.4. Lack of therapeutic efficacy
'Reports of lack of therapeutic efficacy should be collected and recorded when notified and followed-up if incomplete. They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports as applicable (see GVP Module VII).'

VI.B.7.2. Report nullification
'The nullification of a report should be used to indicate that a previously transmitted ICSR is considered completely void (nullified), for example when the whole case was found to be erroneous.'

VI.C.2.2.12. Reporting of off-label use
'If collected in the frame of the routine pharmacovigilance activities, individual reports of off-label use with no suspected adverse reaction should not be submitted to the EudraVigilance database since the minimum criteria for ICSRs validation are incomplete (see VI.B.2. for ICSRs validation).'

Alnylam Global Patient Safety & Risk Management (GPSRM) utilised PV service provider Syneos Health for global ICSR processing services across all sources. Syneos Health operated under GPSRM procedures, and ICSRs were managed within the Alnylam Global Safety Database (GSD). The GPSRM Case Management and Vendor Oversight (CMVO) team was responsible for overseeing service provider activities.

Aspects of case workflow managed by Syneos Health and those managed by Alnylam are indicated below.

Activity	Syneos Health	Alnylam
Receipt of AEs and Other Safety Information	X	
Intake	X	
Triage	X	
Data Entry	X	
QC	X	
Medical Review		X
Finalization	X	
Distribution of expedited reports	X	
Post-Market Reconciliation Activities	X	

Alnylam medical review consisted of a review of every case and activities included, but were not limited to, assessment of expectedness, company causality, confirmation of coding, narrative review, entry of the company comment, and query review.

Follow-up was conducted directly by Alnylam staff or facilitated through Local Safety Officers (LSOs).

A line listing of 12,108 cases across all four UK-authorised products initially received since 01 January 2020 was provided for inspection. Of these, 49 cases were reviewed in more detail.

The following deficiencies were identified with respect to the management and reporting of ADRs:

Finding MA.1 a)
There was late reporting of ICSRs to the MHRA that had not been identified by the company

until the inspection.

i. Serious spontaneous case [redacted] originating from Bulgaria reporting cardiac failure and death with [redacted] was received by the company on 04 January 2023 but was not reported to the MHRA until 07 July 2023, 169 days late.

ii. Non-serious UK spontaneous case [redacted] reporting events of anger, feeling abnormal, and fatigue with [redacted] was received by the company on 19 September 2022 but was not reported to the MHRA until 07 July 2023, 201 days late.

Actions required post-inspection: The MAH should review the impact of this finding on MHRA and EMA reporting and include this information as part of the further assessment and CAPA, where relevant.

[redacted]

[redacted]

[redacted]

Finding MA.1 b)

Cases that did not qualify for regulatory reporting to the MHRA—including outcome-only cases (e.g. death), cases with no identifiable patient, solicited unrelated cases, and special situation cases with no reportable ADRs—were reported in error to the MHRA. Examples included:

Death (outcome-only) spontaneous cases:

i. [redacted] was a report of death (outcome-only case) received by the MAH on 08 August 2022 and incorrectly reported to the MHRA on 12 August 2022.
ii. [redacted] was a report of death (outcome-only case) received by the MAH on 22 July 2022 and incorrectly reported to the MHRA on 01 August 2022.
iii. [redacted] was a report of death (outcome-only case) received by the MAH on 03 March 2022 and incorrectly reported to MHRA on 07 March 2022.

Cases with no identifiable patient:

i. Non-serious spontaneous case [redacted] was received by the MAH on 15 April 2022 and reported to the MHRA on 05 May 2022.
ii. Serious literature case [redacted] was received by the MAH on 03 May 2021 and reported to the MHRA on 13 May 2021.
iii. Serious spontaneous case [redacted] was received by the MAH on 09 May 2022 and reported to the MHRA on 13 May 2022.
iv. Non-serious solicited case [redacted] was received by the MAH on 09 September 2022 and reported to the MHRA on 11 October 2022.

Special situation cases with no ADR:

i. UK compassionate use solicited case [redacted] reported 'off label use' and 'therapeutic product effect incomplete' with [redacted]. No other reactions were reported. Neither term is considered a reportable adverse reaction, and therefore the case should not have been reported to the MHRA. The case was received by the MAH on 18 August 2022 and reported to the MHRA in error on 31 March 2023.
ii. Solicited case [redacted] reported 'off label use' with no ADRs for [redacted] and therefore should not have been reported to the MHRA. The case was received by the MAH on 01 February 2021 and was submitted to the MHRA on 10 March 2021.

Solicited cases with unrelated serious events:

i. [redacted] received by the MAH on 29 January 2021 and reported to the MHRA on 07 February 2021.
ii. [redacted] received by the MAH on 01 March 2021 and reported to the MHRA on 06 March 2021.
iii. [redacted] received by the MAH on 04 January 2021 and reported to the MHRA on 08 January 2021.
iv. [redacted] received by the MAH on 11 January 2021 and reported to the MHRA on 19 January 2021.

The MAH identified these overreporting errors and corrected the database configuration rules on 22 July 2022 and data handling conventions on 25 July 2022 to prevent such cases from being reported. However, the changes were not fully effective as during the inspection, cases

of erroneous reporting after 25 July 2022 were identified, despite corrective actions being completed. Examples are listed above and include:

- Death (outcome-only) case [redacted]
- Case with no identifiable patient [redacted]
- Special situation case [redacted]

Following the identification of the overreporting errors to the MHRA and implementation of corrective actions on 22 and 25 July 2022, the MAH did not conduct a retrospective impact assessment or correction (nullification) of cases historically overreported to the MHRA.

Actions required post-inspection: It was confirmed after the inspection that the MHRA expects cases incorrectly reported to the MHRA to be nullified per GVP VI.B.7.2. Report nullification and VI.C.6.2.2.9. Nullification of cases. The MAH should conduct an impact analysis and share with the MHRA the number of cases impacted and the proposed nullification date of these cases before taking action to correct these reports. The impact on EMA reporting, and subsequent decisions on nullification, should also be considered as part of this response.

[redacted]

[redacted]

Finding MA.1 c)
Cases were identified where required follow-up activities were late or missing, including one case in which a targeted follow-up questionnaire (TQ) had not been sent. i. Case [redacted] from Canada, received by the MAH on 01 October 2021, reported the event 'liver transplant' with [redacted]. Per the RMP for [redacted] (approved in the UK/EU on 19 November 2020), a TQ relating to hepatic events should be sent to the reporter. The MAH was using the standardised MedDRA query (SMQ) 'Hepatic disorder' to define hepatic events requiring targeted follow-up, which included the PT of 'liver transplant'. However, a TQ had not been sent.

ii. Case [redacted] a fatal case with [redacted] from the UK, was received by the MAH on 08 August 2022. The first follow-up was sent on 05 September 2022, which was 18 days later than the 10 calendar days from Day 0 stipulated for follow-up within company procedure [redacted] (version [redacted] effective date 15 July 2022). [redacted] indicated that for SAEs (including fatal cases), three follow-up attempts should be made. However, no subsequent follow-up attempts were made for this case.

iii. [redacted], a case of maternal exposure during pregnancy with [redacted] from the United States, was received by the MAH on 22 September 2022. The first follow-up attempt occurred on 10 October 2022, 8 days later than the 10 calendar days from Day 0 stipulated for follow-up within company procedure [redacted] (version [redacted], effective date 15 July 2022).

[redacted]

[redacted]

Finding MA.1 d)
The MAH of the company's products authorised in Great Britain, Alnylam Netherlands B.V.,

had not been set up on MHRA Gateway and the company transmitted ICSRs using the company name 'Alnylam Pharmaceuticals, Incorporated'. Consequently, the MAH had not received any serious or non-serious case reports via Anonymised Single Patient Reports (ASPRs) from the MHRA as ASPRs would be automatically sent to the entity registered as the UK MAH. A preliminary review at the MHRA indicated that approximately 30 cases from the MHRA had not been downloaded as a result of this issue.

Actions required post-inspection: The company should register on the MHRA Gateway with Alnylam Netherland B.V. and download all ASPR cases. As part of Further Assessment, the MAH should assess the impact on signal detection and on submitted PSURs. The MAH should also check and confirm if any other Regulatory Authority data are not being collected.

[redacted]

[redacted]

MA.2 Collection and collation of solicited sources of safety information

Requirements:

GVP Module I – Pharmacovigilance systems and their quality systems
I.C.1.1. Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the EU
'… the marketing authorisation holder should ensure that mechanisms are in place so that the QPPV receives all relevant information […] in particular on: […]

- *information from sources other than from the specific marketing authorisation holder, e.g. from those with whom the marketing authorisation holder has contractual arrangements;'*

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.1. Collection of individual safety reports
'*[…] marketing authorisation holders should take appropriate measures to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources.*'

VI.B.4. Data management
'When transfer of pharmacovigilance data occurs within an organisation or between organisations having set up contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.'

GVP Module VII – Periodic safety update report (Rev 1)
VII.B.5.9 1. PSUR sub-section "Other clinical trials"
'*This PSUR sub-section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources which are accessible by the marketing authorisation holder during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).'*

The above GVP references should be read in conjunction with the **Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority.**

MHRA Good Clinical Practice Guide ('Grey guide'), Chapter 5, section 5.12
'It is recommended, however, that if the MAH is either supplying the IMP and/or providing funding to the trial, a written agreement is put in place that requires the investigator to report safety information to the MAH, and also requires that the MAH should keep the sponsor/investigator informed of any significant new safety information relating to the IMP during the course of the trial.'

At the time of inspection, there were 17 investigator-initiated studies (IISs) across Alnylam's product portfolio, of which three were completed and 14 were ongoing. Four IISs involved [redacted] as an investigational medicinal product, one of which was interventional, and the remainder were non-interventional studies focused on aspects of related diseases rather than a particular product. Of these, seven studies were reviewed to varying extents as part of this inspection.

The following deficiencies were identified with respect to pharmacovigilance and IISs.

Finding	**MA.2 a)**

The MAH did not have a robust mechanism in place to ensure that all relevant safety data was received from investigator-initiated studies (IIS) to fulfil regulatory requirements within Module VII regarding PSURs and HMR Part 11 regulation 182(4).

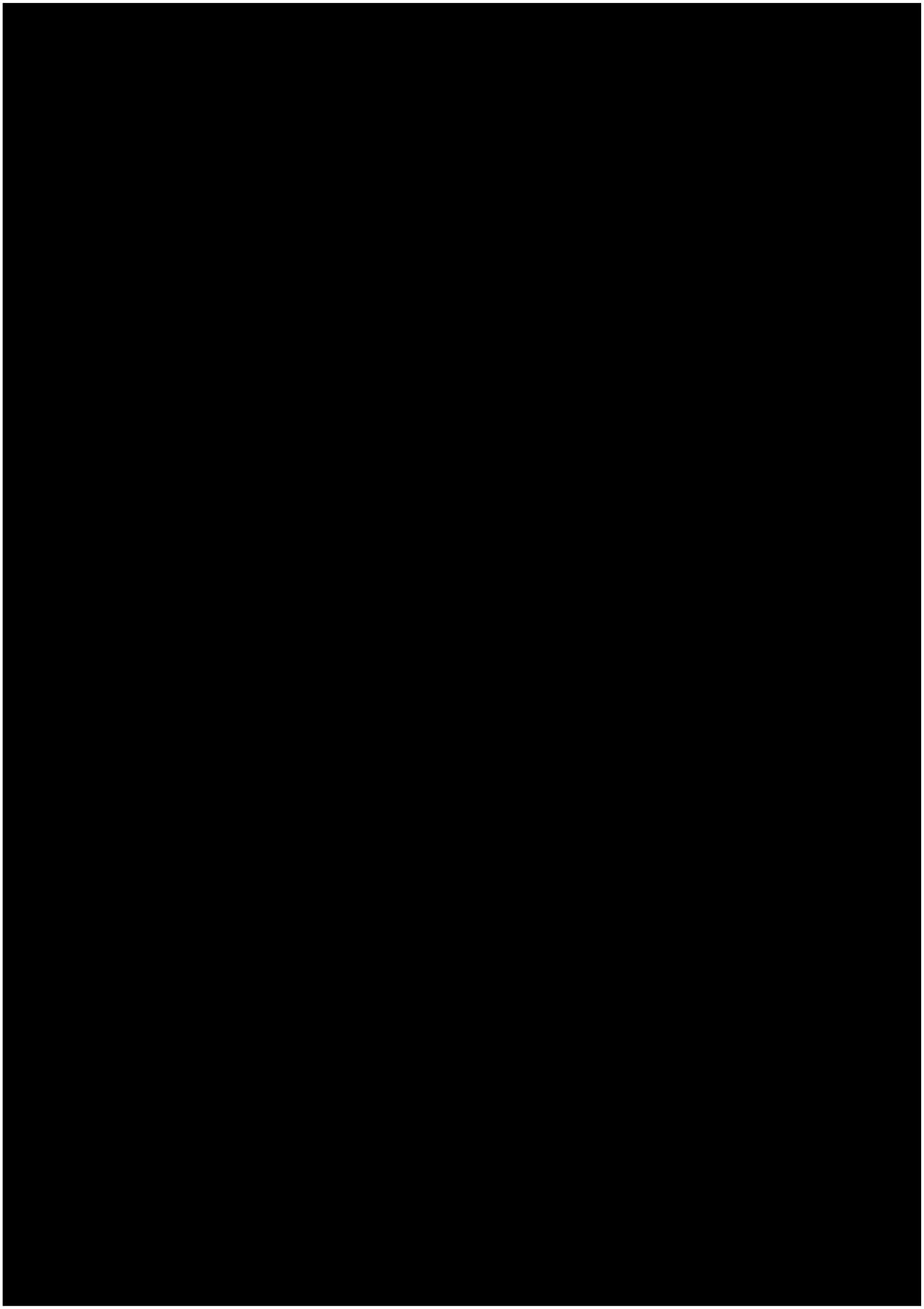
There were seven ongoing non-interventional, non-MAH sponsored studies for which the contracts and agreements did not stipulate the requirement for the transfer of safety data or significant safety issues related to the product between the sponsor (investigator) and the MAH.

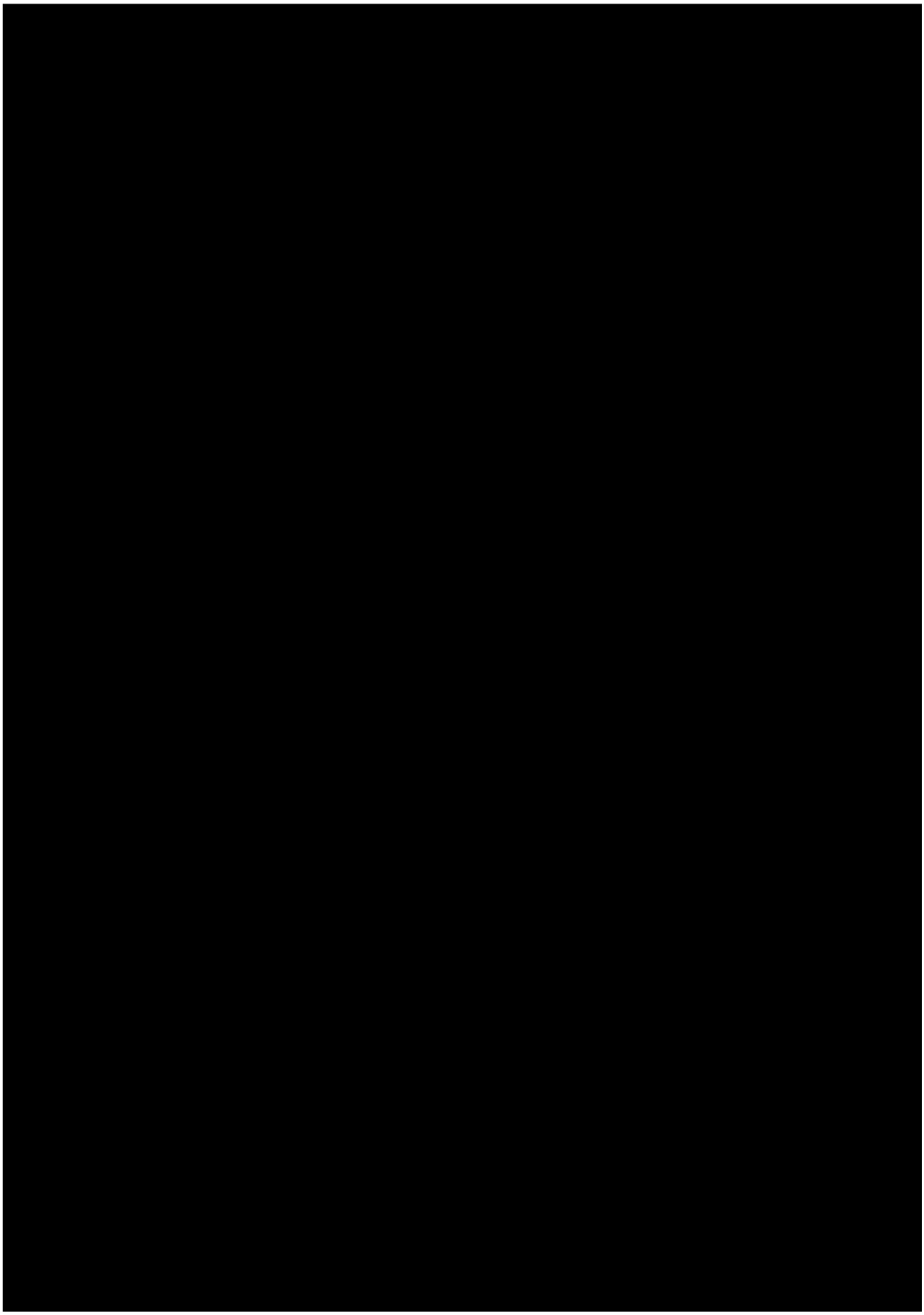
The studies implicated were as follows:
1. [redacted] (130 subjects enrolled)
2. [redacted] (67 subjects enrolled)
3. [redacted] (number of subjects enrolled not available)
4. [redacted] (1152 subjects enrolled)
5. [redacted] (1181 subjects enrolled)
6. [redacted] IMP (500 subjects enrolled)
7. [redacted] (38 subjects enrolled)

The company indicated that they would obtain IIS safety information indirectly from Health Authority downloads. There was a process in place ([redacted], version [redacted], effective date 12 October 2022) in which PrimeVigilance performed daily downloads of ICSRs from Health Authorities including the MHRA, EudraVigilance, DAEN (from TGA), CanadaVigilance, and VAERS and FAERS (from FDA). However, no ICSRs from IISs had been downloaded from the MHRA (see finding MA.1 d)) and this mechanism alone was inadequate to obtain timely information on SAEs as well as non-serious ADRs and AEs.

Actions required post-inspection: As part of Further Assessment, the MAH is requested to perform a complete review of all ongoing IIS contracts to assess whether there is adequate wording to define responsibilities for reporting to health authorities, in addition to transferring reports to the MAH.

[redacted]





[redacted]

[redacted]

Finding MA.2 b)
For IISs with an agreement stipulating safety data to be exchanged between the sponsor and MAH, no mechanisms (for example, reconciliation) were in place to ensure that all safety data had been received by the respective recipient. An example was the ongoing interventional study [redacted], whereby Exhibit C of the amended agreement (effective date: 06 October 2021) included the provision for SAEs and other safety information to be sent to the MAH within 24 hours. However, there was no provision in the agreement for reconciliation activities or confirmation of receipt of pharmacovigilance data between the sponsor and the MAH. The company confirmed no process was in place overall to reconcile safety information received from IISs.

[redacted]

[redacted]

Finding MA.2 c)
For completed IIS [redacted], there was no requirement in the agreement with the sponsor for the final study report or interim reports to be sent to the MAH. The final study report was obtained by the MAH when it was published in Orphanet Journal of Rare Diseases on 8 March 2023, over 8 months after the study ended in quarter 2 of 2022. The MAH also confirmed that interim reports were also not received for this study.

[redacted]

[redacted]

Finding MA.2 d)
There were examples of IISs which were not listed within the relevant section of the annual [redacted] PSUR (DLP 09 August 2022). Section 9.1 'Other Clinical trials and sources' stated that 'During this reporting interval, there is 1 ongoing investigator-initiated study utilizing [redacted] that the MAH is aware of; this study, entitled [redacted] " was initiated in July 2021 in the USA. The MAH did not receive any report of new and important safety information pertaining to [redacted] identified from this study during this reporting interval.' However, at the time of the PSUR authoring, an additional 3 ongoing IISs should have been included: [redacted] (started 25 January 2019), [redacted] (started 17 April 2021) and [redacted] (started 18 February 2021).

[redacted]

C.4.3 Minor findings

MI.1 Management of and reporting of adverse reactions

Finding MI.1 a)
The Alnylam Always Serious List (AASL) (version , effective date 30 December 2021) was not maintained in accordance with internal procedures and had not been reviewed since its effective date. The AASL was used by Alnylam to identify medically serious events and was configured within the global safety database to automatically identify the terms on the list as serious events. Per procedure (version , effective date 23 June 2023), section 7.5.3.3 will be reviewed by MSRM physicians in conjunction with annual MedDRA updates to ensure the list remains up to date with appropriate terms (see).' The EMA MedDRA IME list current at the time of inspection was aligned to MedDRA version and was released on 22 March 2023 but the company had not reviewed the AASL against this current IME list for potential new or removed terms and had not conducted an annual review per internal company procedures. The company indicated that there was an ongoing project to update and align the AASL to the EMA IME list; however, there was no official project documentation available at the time of inspection.

[redacted]

Finding MI.1 b)
The Expected Term List (ETL) for [redacted] used to configure auto expectedness of AEs within the database, had a missing event of 'rash macular'. The event was included in the previous version of the list [redacted] The company confirmed that this had been missed due to a transcription error when creating the updated ETL. It was confirmed that no cases involving the PT 'rash macular' had been received since the new ETL had been configured.

[redacted]

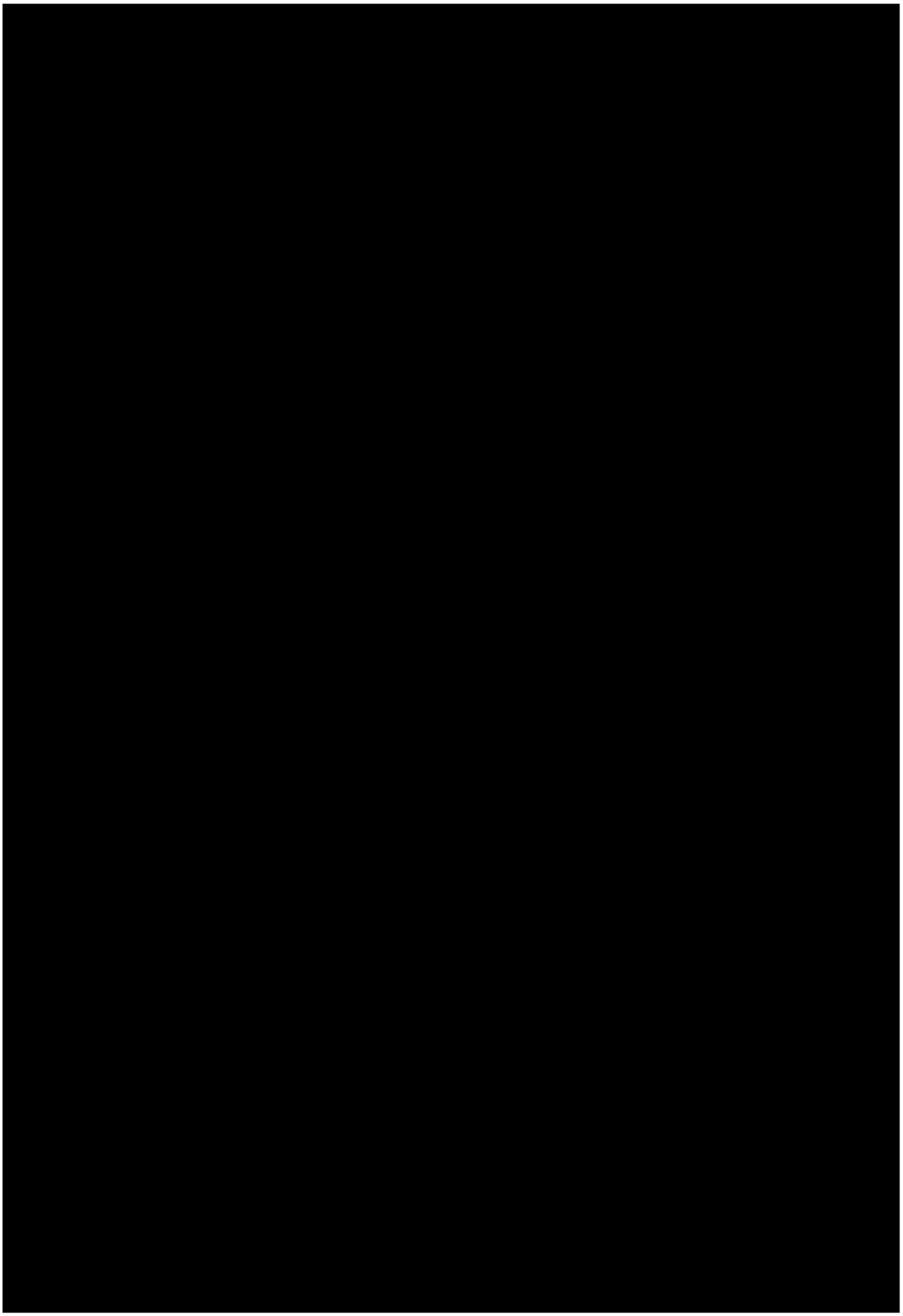
Finding MI.1 c)
Cases were identified where data entry errors had occurred. i. [redacted] cases [redacted] and [redacted] were reported from studies but no protocol ID had been entered into the relevant global safety database field. ii. [redacted] cases [redacted] and [redacted] were reported from a patient support programme but no protocol ID had been entered into the relevant global safety database field.

iii. The PT of renal transplant was not coded in [redacted] case [redacted] where the verbatim text stated 'In May 2022 the patient underwent Kidney Transplantation (KTx).'

iv. Case [redacted] from a [redacted] expanded access programme was received by the company on 17 May 2023. During case entry, the initial received date was incorrectly captured as 17 May 2022 instead of 17 May 2023.

There was no impact on expedited reporting as a result of these errors, but the MAH should confirm whether there was any impact on data included within the relevant PSURs.

[redacted]



[redacted]

[redacted]

Finding MI.1 d)
For IIS where the investigator was responsible for Regulatory Authority (RA) reporting, the MAH had not configured the global safety database to ensure that ICSRs received from IISs and which met reporting requirements to RAs were not submitted by the MAH. As such, there were insufficient measures in place to prevent duplicate reporting. No such cases were identified, hence this is graded as a minor finding.

[redacted]

[redacted]

Finding MI.1 e)
A procedural requirement, whereby Global Safety Systems (GSS) should notify the SRMT Chair and CMVO upon configuration of Targeted Questionnaires (TQs) in the GSD, had not been followed for the [redacted] Ocular Events TQ and hence the SRMT Chair did not have confirmation that the action had been completed. Per [redacted] (version [redacted] effective date 17 October 2022) section 7.2.13 'GSS confirms the list of PTs/SMQs and TQ forms are configured in the GSD and informs the SRMT Chair and the CMVO of the updates made to GSD within 5 business days.'

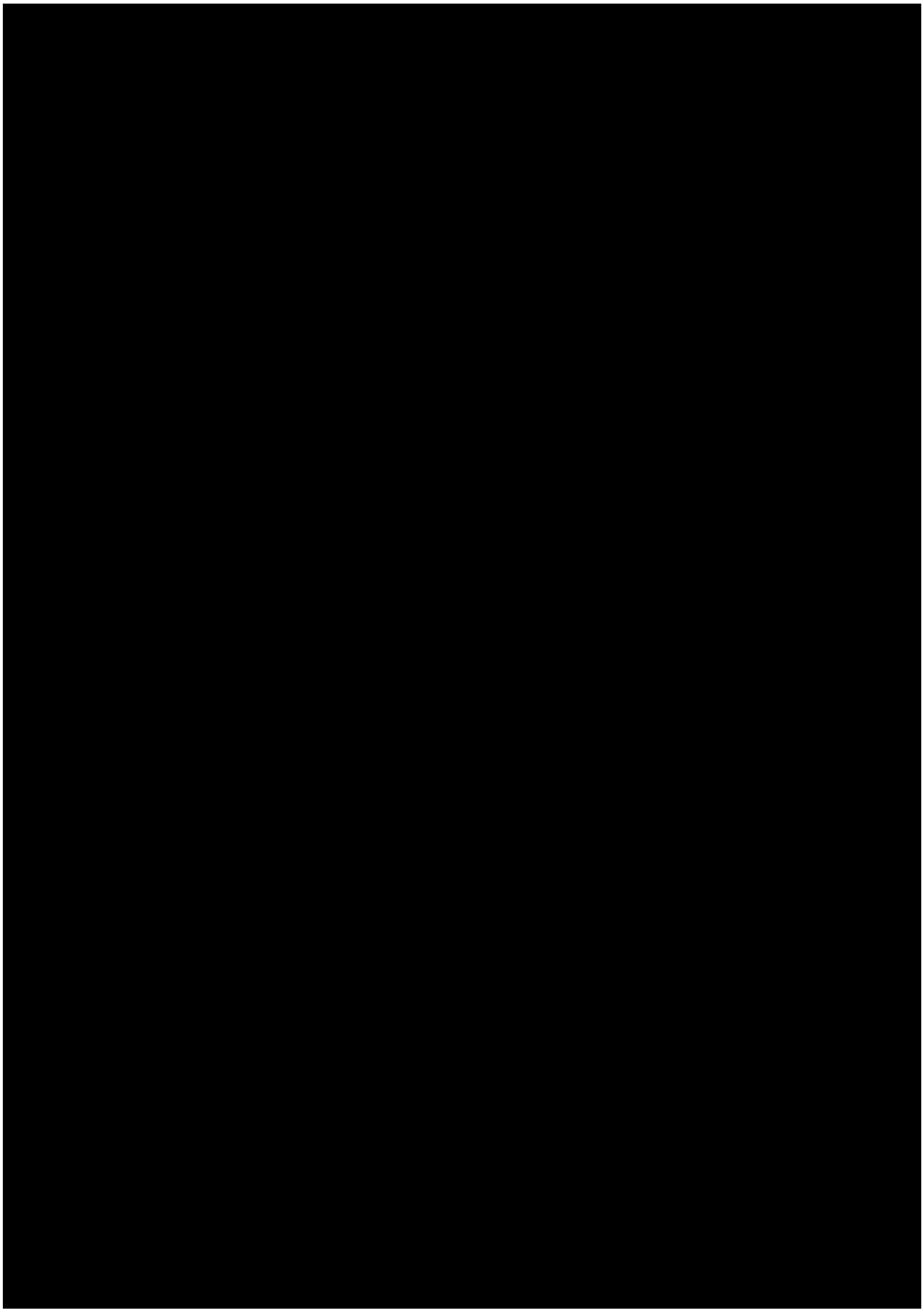
[redacted]

[redacted]

MI.2 Signal management

Finding MI.2 a)
Procedural documents such as SOPs, work instructions or guidelines for signal management activities lacked detail on certain aspects of the process; however, this was minor in nature as the activities carried out in practice were not impacted. i. The work instruction [redacted]' (version [redacted] effective date 14 January 2022) detailed that safety observations could be identified across multiple sources, but there was no procedure detailing how the sources of safety data could be retrieved/accessed, and how frequently, by the Safety Risk Management Team (SRMT) Chair who was responsible for the review and triage of all safety related information. ii. The rationale for the methodology and frequency of signal detection activities was not detailed in any procedural documentation. iii. It was stated during interview that any signals potentially related to the mode of action of the product technology (for example, due to Alnylam's novel RNA interference [RNAi] technology) would be discussed at the SRMT Chairs meeting. However, how technology-related signals were identified (e.g. the potential sources of signal information), and how these would be assessed during signal assessment was not specified within a procedural document. Alnylam is reminded of the requirements in GVP module IX.B.5 Quality requirements, which state that '*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 […] Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities.*'

[redacted]



Finding MI.2 b)
There was no documentation to demonstrate the SRMT Chairs meeting for February, March and May 2023 had been conducted as no official outputs from the meeting were routinely produced. Per [redacted] (version [redacted] effective date 14 January 2022) and [redacted]' (version [redacted], effective date 23 July 2021), the SRMT Chairs meeting occurred monthly to review the signal tracker and exchange safety information. However, the MAH could not provide evidence that these meetings had occurred, as the procedures did not define the need for meeting minutes to be taken.

[redacted]

MI.3 Post-authorisation safety studies

Finding MI.3 a)
The MAH did not have a process in place to identify whether IISs financed by the MAH met the definition of a PASS. No examples of a missed PASS were identified during the inspection; however, as part of the response the company should complete a full impact assessment. The MAH should note that per GVP Module VIII – Post-authorisation safety studies (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), VIII.A. Introduction, *'Non-interventional PASS concerned by this guidance are those initiated, managed or financed by a marketing authorisation holder voluntarily or pursuant to an obligation imposed by an EU competent authority'*. Furthermore, per GVP Module I – Pharmacovigilance systems and their quality systems, (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), I.C.1.3. Role of the qualified person responsible for pharmacovigilance for UK authorised products, *'specific additional responsibilities of the QPPV should include: […] being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the UK or pursuant to a risk management plan agreed in the UK'*.

[redacted]

[redacted]

MI.4 Quality management system

Finding MI.4 a)
GPSRM were not informed of the [redacted] PSP programme in Canada prior to initiation of the programme on 04 April 2022. Per [redacted] (version [redacted], effective date 23 July 2021), section 7.12, GPSRM should be informed of a PSP prior to initiation. GPSRM was informed indirectly of the [redacted] PSP via the Local Safety Officer (LSO) May 2022 monthly report, but no other communications were sent. As part of the Further Assessment, the MAH should describe the impact of not following the SOP (for example, GPSRM were unable to review and confirm PV contracts and arrangements for the study).

[redacted]

[redacted]

MI.5 Pharmacovigilance system master file

Finding MI.5 a)
The PSMF (version [redacted], effective date 30 April 2023) did not contain any ICSR quality compliance metrics, even though these were collected by the company. Per GVP II.B.4.6. PSMF section on pharmacovigilance system performance, '*The PSMF should include a description of the monitoring methods applied and contain as a minimum […] A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance.*'

[redacted]

C.4.4 Comments

1. The procedure for oversight of workflow / ageing reports of the global safety database was documented in a set of training slides rather than a work instruction or guidance. For a consistent approach, the company should consider formalising this process as part of the QMS.

2. [redacted]' (version [redacted] effective date 02 December 2020) did not specify timeframes in which reconciliation should be completed and finalised following conduct in accordance with agreements. No examples with concerning timelines were identified during inspection and therefore this has been raised as a comment only.

3. [redacted])' (version [redacted] effective date 07 July 2023) described the monthly ICSR sample review activity performed by Alnylam for data entry quality checks. The work instruction stated that 'Source documentation data will be reviewed against structured fields in the GSD and results of the review will be documented using the ICSR Data Quality Monitoring Report Form, [redacted].' However, in practice it was confirmed that this form was not used, and instead a spreadsheet was created each month to document the check of all structured fields. It is recommended that the procedural document is updated to reflect activities occurring in practice.

4. Meetings occurred monthly between the MAH and case processing service provider Syneos to review service provider case processing KPIs; however, meeting minutes did not capture who was present during the meeting. It was therefore not possible to evidence whether MAH representatives were present during the meetings. The MAH indicated that a request had been made to Syneos to document attendees going forward.

5. There was an error in the recording of the closure date for the signal of 'Mild transaminase elevations' with [redacted] in the legacy signal tracker. The tracker indicated that the status of the signal was open (ongoing) but a date of closure had been recorded as 08 February 2023 (date of the SRMT meeting). Furthermore, the minutes of the SRMT meeting 08 February 2023 detailed the decision to keep the signal open (ongoing) with analysis to be presented in the next PBRER (DLP 09 August 2023). The company confirmed that the signal remained open and the date of closure was recorded in the tracker by error. It was noted that this legacy tracker was decommissioned on 24 March 2023 and replaced by [redacted] which was in effect at the time of inspection, and the signal record on [redacted] accurately indicated the signal was open (ongoing).

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.

The MAH is encouraged to share this inspection report with relevant service providers to whom it has sub-contracted pharmacovigilance activities. Service providers are reminded that deficiencies that are more broadly applicable to MAHs not subject to this inspection may need to be shared with those affected, such that appropriate CAPA can be derived. The service provider and MAH(s) affected should be able to demonstrate effective assessment and resolution of deficiencies that have been reported during any inspection.

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”.
- MHRA Good Clinical Practice Guide (‘Grey guide'), 2012.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBD	**DATES**	10 – 13 July 2023
PHARMACOVIGILANCE INSPECTION OF	Alnylam Netherlands B.V.	**START TIME**	09:00 BST
LOCATION	Day 1: Remote Days 2 to 4: Onsite at Alnylam Pharmaceuticals, Braywick Gate, Braywick Road, Maidenhead, Berkshire SL6 1DA.	**INSPECTION TEAM**	[redacted] (Inspection Lead), [redacted], Claire Longman

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

- Collection and collation of pharmacovigilance 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. Demonstration of 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 inspectors 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 document requests will be submitted throughout the course of the inspection.

Monday 10 July 2023 (Day 1, remote)	
Document review 09:00 – 11:00 BST	Inspectors only

Opening Meeting – Remote via Zoom 11:00 – 11:30 BST, led by [redacted] Agenda: • Introductions • Review of inspection logistics and plan • **Company Presentation.** The MAH is requested to provide an overview of the company's PV system with a focus on the topics above and the quality systems supporting these topics (to last no longer than 20 minutes). Please highlight any relevant ongoing remediation work on the PV system and any significant recent or upcoming changes to the pharmacovigilance system.	Company attendee(s): • [redacted] – Director, PV QA • [redacted] – Director, R&D/PV QA • [redacted] – UK National Contact Person for Pharmacovigilance • [redacted] – SVP, Global Patient Safety & Risk Management • [redacted] – EU/UK QPPV • [redacted] – VP, UK and Ireland Country Manager
Document review 11:30 – 14:00 BST	Inspectors only
Session 1 - Collection and collation of pharmacovigilance data **14:00 – 15:30 BST** *(remote session)* Including but not limited to: • Solicited sources • Reconciliation • Management of contracts and agreements (PVAs/SDEAs)	Interviewee(s): • [redacted] – SVP, Global Patient Safety & Risk Management • [redacted] – Senior Director, Medical Research • [redacted] – Director, Global Patient Safety & Risk Management • [redacted] – Sr. Manager, Early Access • [redacted] – Insights and Analytics • [redacted] – Director, Global Patient Safety & Risk Management • [redacted] – Director, Medical Information • [redacted] – Senior Manager, Global Patient Safety & Risk Management • [redacted] – Sr Manager, Global Patient Safety & Risk Management
Document review 15:30 – 17:00 BST	Inspectors only

Tuesday 11 July 2023 (Day 2, onsite)	
Document review 09:00 – 14:00 BST	Inspectors only
Session 2 - Management and reporting of ADRs **13:00 – 14:30 BST** Including but not limited to: • Data entry, case processing and assessments • Case quality in the safety database • Expedited reporting of ICSRs • Follow-up activities MAH is requested to provide a demonstration of the safety database during this session, in order to demonstrate core steps of the process.	Interviewee(s): • [redacted] – Director, Global Patient Safety & Risk Management • [redacted] – Director, Global Patient Safety & Risk Management • [redacted] – EU/UK QPPV • [redacted] – Manager, Global Patient Safety & Risk Management • [redacted] – Director, Global Patient Safety & Risk Management
Session 3 – Signal Management **15:00 – 16:30 BST** Including but not limited to: • Signal detection, validation and evaluation activities • Quality requirements MAH is requested to provide a demonstration of Empirica Signal during this session.	Interviewee(s): • [redacted] – Executive Director, Global Patient Safety & Risk Management • [redacted] – Director, Global Patient Safety & Risk Management
Document review 16:30 – 17:30 BST	Inspectors only
Wednesday 12 July 2023 (Day 3, onsite)	
Document Review 09:00 – 17:30 BST	Inspectors only

Ad hoc discussions Inspectors will arrange ad hoc discussions, if required.	Attendee(s): • TBD
Thursday 13 July 2023 (Day 4, onsite)	
Document Review 09:00 – 17:30 BST	Inspectors only
Ad hoc discussions Inspectors will arrange ad hoc discussions, if required.	Attendee(s): • TBD
Closing meeting (timing to be confirmed) Verbal feedback will be provided from the inspection. All relevant personnel are welcome to attend the closing meeting.	Attendees: • [redacted] – Director, PV QA • [redacted] – Director, R&D/PV QA • [redacted] – UK National Contact Person for Pharmacovigilance • [redacted] – SVP, Global Patient Safety & Risk Management • [redacted] – EU/UK QPPV • [redacted] – VP, UK and Ireland Country Manager

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 also list the inspection host, if different.

Designated contact point/inspection host and contact details:

[redacted] – Director, PV QA
Alnylam Pharmaceuticals
Braywick Gate,
Braywick Road
Maidenhead United Kingdom SL6 1DA
United Kingdom
[redacted]
Work: [redacted]
Mobile: [redacted]