Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Chiesi Farmaceutici S.p.A.

MHRA Inspection Number: Insp GPvP 8829/11972952-0004

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
aRMM	Additional Risk Minimisation Measures
CAPA	Corrective and Preventative Action
CFT	Cystic Fibrosis Trust
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organisations of Medical Sciences
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GPV	Global Pharmacovigilance
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MENA	Middle East and North Africa
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PSMF	Pharmacovigilance System Master File
PT	Preferred Term
PV	Pharmacovigilance
QA	Quality Assurance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SER	Signal Evaluation Report
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System(s) inspected:	Chiesi Farmaceutici S.p.A., [redacted]
Site(s) of inspection:	Remote inspection
Main site contact:	[redacted]
Date(s) of inspection:	20 – 21 August and 02 – 04 September 2020
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	28 – 30 March 2011
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Name and location of EU QPPV:	[redacted]
Global PV database (in use at the time of the inspection):	Oracle Argus (commercially available)
Key service provider(s):	Parexel International Ltd. provided global case management activities for post-marketing and clinical trials.
Inspection finding summary:	4 Major findings 3 Minor findings
Date of first issue of report to MAH:	28 September 2020
Deadline for submission of responses by MAH:	02 November 2020 Clarifications due 04 December 2020
Date(s) of receipt of responses from MAH:	02 November 2020 Updated responses received 04 December 2020
Date of final version of report:	09 December 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Chiesi Farmaceutici S.p.A. was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable 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.

Chiesi Farmaceutici S.p.A. (hereafter referred to as Chiesi) is a global pharmaceutical company headquartered in Parma, Italy. The company product portfolio comprises a range of products licensed via centralised and national procedures, and focuses on respiratory, neonatology and rare diseases therapeutic areas.

The global pharmacovigilance (GPV) team is based in Parma, which is also the site of the PSMF and EU QPPV. A number of affiliate pharmacovigilance units feed into GPV, and are separated into three regions, Region Europe, which includes the UK affiliate (Chiesi Ltd.), Region U.S.A. and Region Emerging Countries & IMDD.

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance systems and was performed remotely due to the Covid-19 pandemic. No formal interview sessions were scheduled, with the inspection primarily taking the form of document review (including outputs from the global safety database). Ad hoc teleconferences were held with subject matter experts as necessary. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

Areas regarding the maintenance of reference safety information, periodic safety update reports 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.

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B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] 31 March 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, details of which are 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 was held via teleconference to review the inspection findings on 04 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 since 2011.

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 Implementation of additional risk minimisation measures

Requirements:

Directive 2001/83/EC as amended
Article 104(2) and Article 104(3)(c)

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance,
Regulation 182 (2) *"The holder must (as part of its pharmacovigilance system)—*
(c) operate a risk management system for the product in accordance with the risk management plan (if any) for the product [...]"

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)
XVI.C.2. *"The measures adopted in the RMP should be implemented by the marketing authorisation holder at national level after agreement with the national competent authorities.*

The applicant or marketing authorisation holder should provide information regarding the status of implementation of additional risk minimisation measures as agreed with the national competent authorities and keep them informed of any changes, challenges or issues encountered in the implementation of the additional risk minimisation measures. Any relevant changes to the implementation of the tools should be agreed with the national competent authorities before implementation."

Commission Implementing Regulation (EU) No. 520/2012
Article 12(1) *"Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents […]."*

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. The majority of safety concerns are addressed by routine risk minimisation measures. Exceptionally, for selected important risks, routine risk minimisation may be considered insufficient and additional risk minimisation measures (aRMMs) may be deemed necessary.

The following finding was identified in relation to the implementation of aRMMs:

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Finding MA.1 a)

There was a failure to disseminate educational materials in line with the MHRA-agreed distribution plan for [redacted] and a failure to inform the MHRA of redistribution of educational materials for [redacted]

i) [redacted]

The [redacted] educational materials consisted of a safety checklist for prescribing physicians that outlined the risks of teratogenicity, and the requirements to check for hypersensitivity to [redacted] to monitor cysteine levels and to arrange three-monthly check-ups.

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Educational materials were initially agreed with the MHRA in 2015 by the previous MAH, [redacted] now [redacted] Upon change of ownership and in line with the renewal application, Chiesi resubmitted the materials, which were approved by the MHRA, along with the associated distribution plan, in January 2019.

However, educational materials were not distributed, despite patients in the UK receiving the product. These patients were continuing from a post-marketing study that had been initiated by [redacted] and closed prior to transfer of the marketing authorisation to Chiesi. As per the agreed distribution plan, educational materials should have been distributed to the 13 centres in the UK that treat cystinosis prior to the product being available on the market.

It was only during pre-inspection preparation that Chiesi identified patients had been receiving the product. It is acknowledged that Chiesi raised a CAPA record [redacted] on 10 August 2020 and initiated a risk assessment on 18 August 2020. It was confirmed that the materials had been sent in line with the distribution plan at the time of the inspection.

[redacted]

The [redacted] educational materials consisted of an educational pack for healthcare professionals aimed at reducing the potential of dosing errors, prescribing errors and dispensing errors; and a patient card that informed patients not to switch between brands due to differing release rates between [redacted] products.

The educational materials and associated distribution plan were agreed with the MHRA in 2015, and the materials were distributed prior to product launch in 2015 in line with the agreed distribution plan. However, in 2017, Chiesi redistributed the educational materials without seeking prior approval from the MHRA.

Chiesi had planned two 'phases' for the mailing house to send the materials in 2015: phase one targeting secondary care and phase two targeting primary care. In 2017, an audit of the UK affiliate identified that there was no evidence that the phase two materials had been distributed. The mailing house subsequently confirmed that the phase two mailing had not occurred in 2015. The CAPA for this audit finding included the distribution of materials to phase two recipients and a redistribution to phase one recipients in 2017 to ensure everyone had received the materials, as well as an investigation to understand what had happened. This investigation revealed documentation that demonstrated the materials had indeed been disseminated in line with the distribution plan in 2015.

Chiesi failed to contact the MHRA following the audit when it was believed that the materials had not been distributed, nor sought approval for the subsequent distribution to phase two recipients and redistribution to phase one recipients.

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]

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[redacted]

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

MA.2 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.*

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event."

Article 107(4) *"Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports."*

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

In line with ICH-E2D, the term 'identifiable' refers to the possibility of verification of the existence of a patient based on the available information. […]

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission as ICSR. Competent authorities and marketing authorisation holders are expected to exercise due diligence in following-up the case to collect the missing data elements and follow-up activities should be documented."

VI.B.5. Quality management
"Competent authorities and marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR submission and case archiving (see VI.C.6.2.4. and GVP Module I for EU guidance on data quality of ICSRs).

Correct data entry, including the appropriate use of terminologies (see VI.B.8. for ICSRs content and format), should be quality controlled, either systematically or by regular random

evaluation. Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. With regard to this, the source data (e.g. letters, emails, records of telephone calls, which include details of an event) or an image of the source data should be easily accessible. The whole process should be monitored by quality assurance audits."

Commission Implementing Regulation (EU) No. 520/2012
Article 11(2) *"Where a marketing authorisation holder has subcontracted some of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks."*

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Finding MA.2 a)

Two examples of valid ICSRs were identified that had not been submitted to EudraVigilance:

- [redacted] Serious spontaneous case from the UK initially received on 29 December 2018, and reported the event PTs angina pectoris, chest discomfort and dyspnoea, with [redacted]
- [redacted] Non-serious spontaneous case from Italy initially received on 08 October 2019, and reported the event PT haemorrhoids, with [redacted].

It was confirmed during the inspection that these ICSRs were not submitted to the EMA by mistake. Review of the output from the global safety database (inspection request A12) revealed a large number of cases that had not been reported to the EMA yet appeared to meet the reporting requirements. A selection of cases was sampled during the inspection, and although sufficient rationale was provided by the MAH for the majority of sampled cases, a full impact assessment should be completed as part of the responses to the inspection report and robust CAPA should be proposed.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

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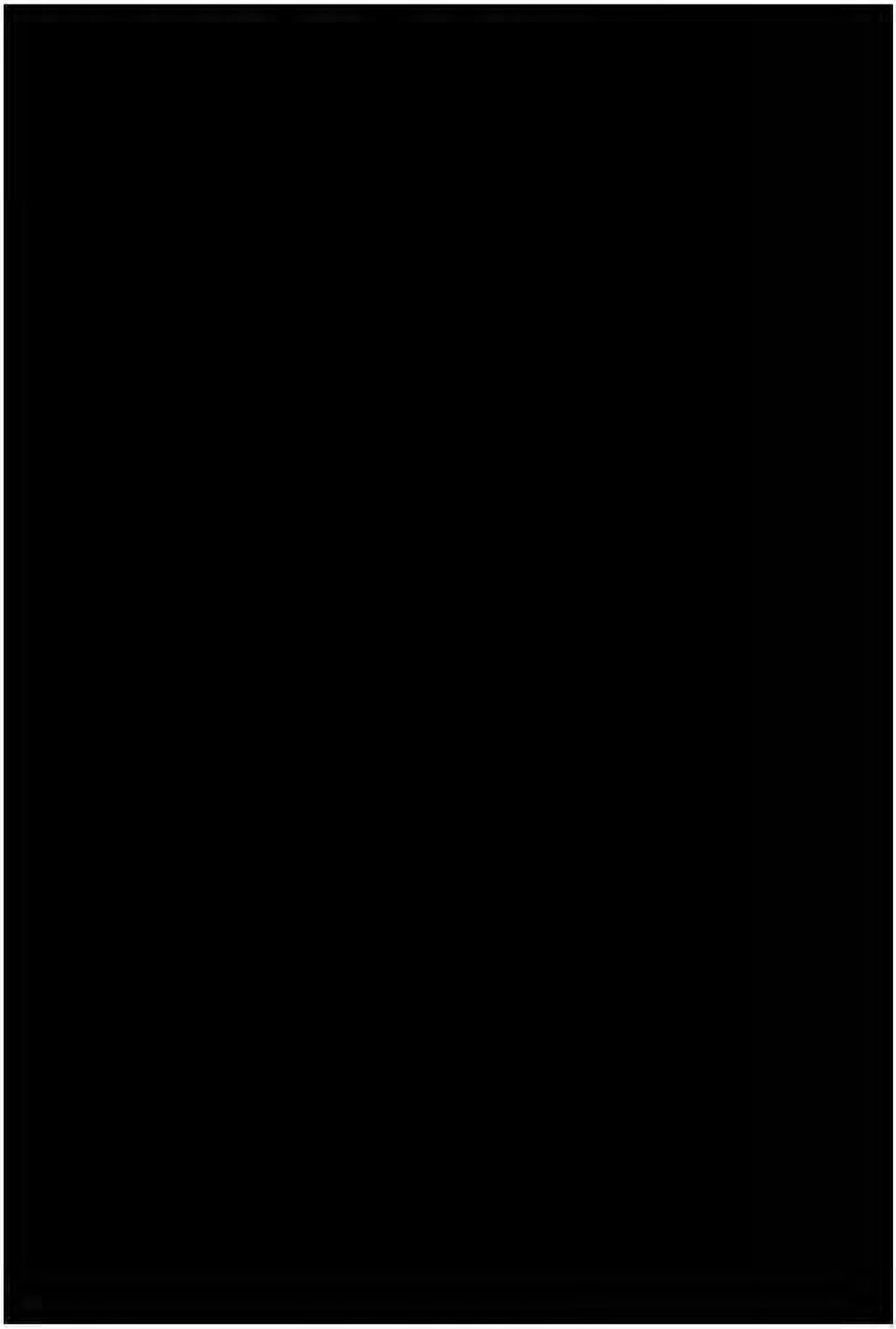

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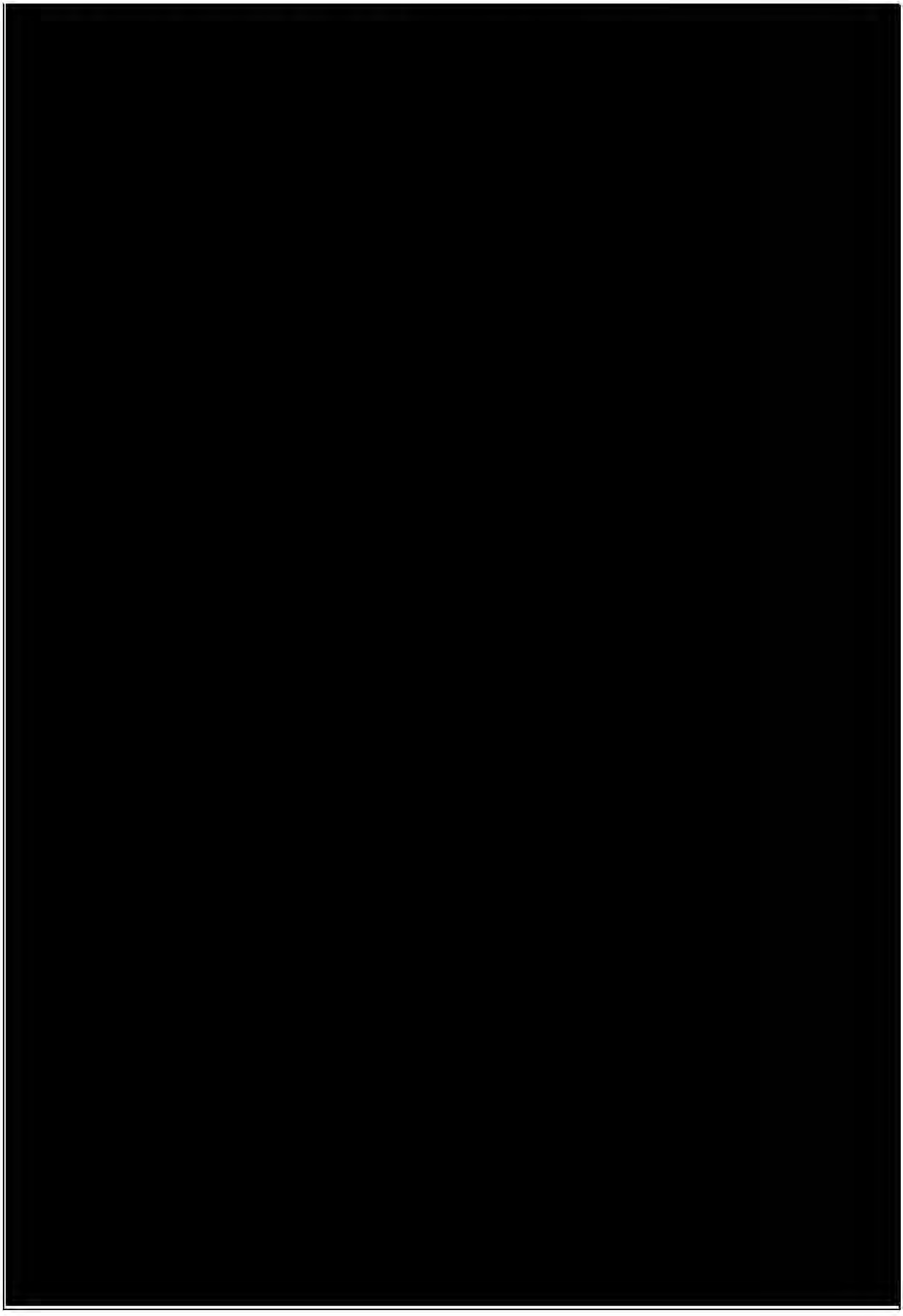

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[redacted]

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

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Finding MA.2 b)

Chiesi had no mechanism to ensure the correct data entry, including the appropriate use of terminologies, for ICSRs that were received in a territory where [redacted] was the MAH and was responsible for ICSR processing.

Chiesi held the marketing authorisation of the products [redacted] and [redacted] in the EEA and in the MENA territories. The products had been licensed to Chiesi by [redacted] the licensor, who held the marketing authorisation in all other territories. Both parties were responsible for the processing of ICSRs originating in their respective territories and ensuring reporting requirements were met for the products in their respective territories. As such, Chiesi was responsible for the submission of serious ICSRs originating in [redacted] territories to EudraVigilance.

Exchange of ICSRs was facilitated through the provision of CIOMS I or XML files, which was used as the source documentation by the receiving party. Original source documentation was only provided on request.

On receipt of a CIOMS I form, Chiesi conducted manual data entry into its safety database, and quality control checks were performed against the CIOMS I form. However, there were no mechanisms in place for Chiesi to ensure correct data entry against original source data. It was stated that [redacted] had its own processes for quality control of the data entry; however, Chiesi did not routinely receive the [redacted] 'ICSR/SAE Quality Check' sheet or 'Medical Evaluation Form' as part of the ICSR exchange.

Additionally, this process was not monitored by quality assurance audits. Chiesi's pharmacovigilance audit strategy had assigned [redacted] a risk score of four (audit frequency of 60 months); there had not been an audit of [redacted] in the previous five years, and the next audit was scheduled for 2024. As a business partner that performed critical pharmacovigilance processes for products subject to additional monitoring, this audit frequency was not considered to be appropriate.

Root Cause Analysis

[redacted]

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[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

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[redacted]

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

Finding MA.2 c)

The following deficiencies were identified in relation to the request for follow-up information of invalid adverse event reports without patient identifiers:

- Case [redacted] Serious spontaneous case from Germany received on 09 April 2018 from a physician who reported that *"one of her patients was under treatment with* [redacted] *and died due to flu"*. The event was initially stated to be unrelated to the treatment with [redacted] Follow-up information was requested; however, this did not include a request for patient demographics. The follow-up information received upgraded the event causality to related. No further follow-up requests were sent to obtain the information required for validation.

- Case [redacted] Non-serious spontaneous case from the UK received on 21 May 2019 from a nurse who reported "*patients were more breathless on* [redacted] No follow-up was sent to obtain the information on patient demographics. Section [redacted] of [redacted] Management of ICSR follow-up requests' [redacted] 08 November 2019) stated *"For non-serious expected cases, the follow-up attempts are not required as long as the four minimum criteria for the case are satisfied"*.

Review of the output from the global safety database (inspection request A12) highlighted a considerable proportion of invalid reports that appeared to not contain patient identifiers, and as such a full impact assessment should be completed as part of the responses to the inspection report.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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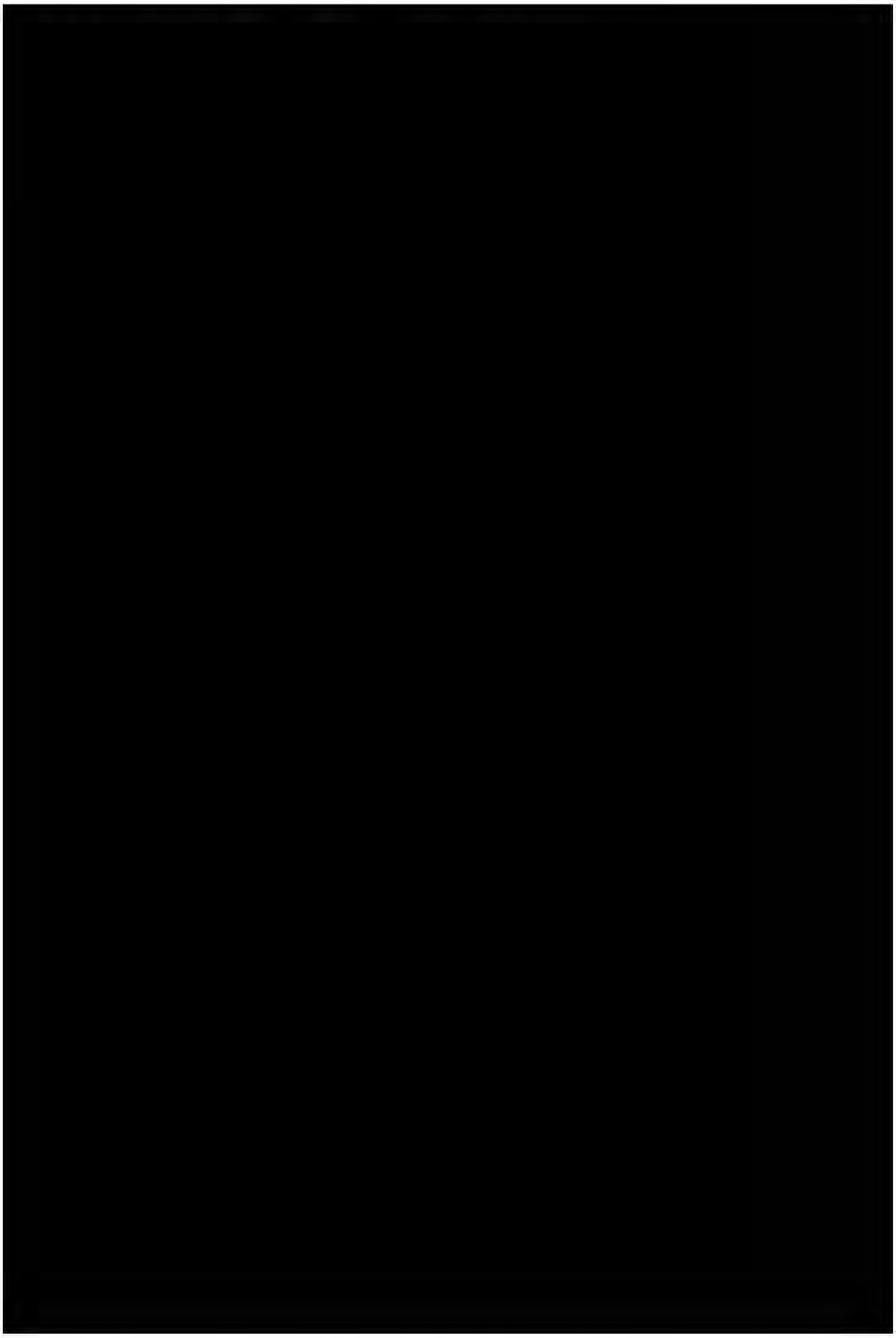

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[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Section 43

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

MA.3 Signal management for biological medicines

Requirements:

GVP Product- or population-specific considerations II: Biological medicinal products [redacted].B.4. Signal Management

"Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological and important differences between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change) […]"

Denominator data and data of suspected adverse reactions (see GVP Module IX) should be analysed to support continuous signal detection and particularly detection of any apparent changes in suspected adverse reaction reporting rates or trends that could indicate new signals (particularly following manufacturing changes) […]

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

GVP Product- or population-specific considerations II: Biological medicinal products (GVP [redacted]) was first published on 15 August 2016 to address several specific challenges in pharmacovigilance that are associated with biological medicinal products.

The following finding was identified in relation to signal management for biological products:

Finding MA.3 a)

The MAH was not undertaking any additional activity for the signal management of biological medicinal products in order to comply with the requirements outlined in GVP[redacted]. Chiesi held the marketing authorisation for [redacted] a biological product indicated for the treatment of respiratory distress syndrome in new-born babies.

The following deficiencies were identified:

- There were no processes in place to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological or to detect important differences between batches. Chiesi was not conducting any trending during signal detection using batch numbers for [redacted] nor using any exposure figures to understand the differences between batches on the market.

- There were no processes in place to ensure signals for biological products were evaluated in the context of batch-specific exposure data.

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Root Cause Analysis

[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]	

MA.4 Pharmacovigilance audit

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 3 *"The pharmacovigilance system master file shall have an Annex containing the following documents: […]*

(5) a list of all scheduled and completed audits;"

Article 13(2) *"Corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. A report on the results of the audit shall be drawn up for each audit and follow-up audit. The audit report shall be sent to the management responsible for the matters audited. The dates and results of audits and follow-up audits shall be documented in accordance with the second subparagraph of Article 104(2) of Directive 2001/83/EC."*

Directive 2001/83/EC (as amended)
Article 104(2) *"The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed."*

The quality assurance auditing of the pharmacovigilance system was not specifically reviewed during this inspection. However, review of pharmacovigilance audit in the context of oversight of non-interventional PASS identified the following findings:

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Finding MA.4 a)

There was a delay of eight months in issuing an audit report relating to the audit of the [redacted] non-interventional category [redacted] in which three major findings were identified. This represented a significant delay in the investigation of non-compliance and implementation of appropriate CAPA.

An audit of the [redacted] managed by the [redacted] was conducted on 25 – 26 November 2019 [redacted] The objectives of the audit were to evaluate the quality systems established by [redacted] and its capability to manage study activities as per the protocol and the agreement with the MAH. However, the audit report was not finalised until 22 July 2020, eight months after the end of the audit.

According to Corporate Procedure [redacted] 'Pharmacovigilance Audits' ([redacted] 19 December 2018), audit reports should be issued within 30 calendar days following the end of an audit.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

[redacted]	

Finding MA.4 b)
The audit of the [redacted] conducted on 25 – 26 November 2019 had not been recorded in the Chiesi PSMF Annex G Quality System 'Table 25 – Pharmacovigilance audits in the last 5 years' [redacted] Additionally, the three major open audit findings identified during the audit had not been recorded in the Chiesi PSMF Section 7 Quality System 'Table A – List of critical and major non-conformities arisen during the performed audits and currently open' [redacted]).

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Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

C.4.3 Minor findings

MI.1 Procedural documentation

Finding MI.1 a)
There was no written procedure that described how oversight of non-interventional studies, in terms of collection and reporting of AE/SAEs, was maintained for products where Chiesi was the MAH. In response to inspection request D3 (*"For study [redacted] please describe the oversight measures that Chiesi has over the collection of data in the UK Registry Database"*), the MAH stated that the oversight activity adopted by Chiesi was consistent with section 7.3 of [redacted] 'PASS' ([redacted] 08 November 2019). However, section 7.3 of [redacted] described the processes for approval and submission of progress reports and interim reports of study results. The company is reminded that the conduct of non-interventional studies, including PASS, form part of the critical pharmacovigilance processes referenced in GVP [redacted], and as such the company should formally define how study oversight will be achieved, particularly for studies imposed as an obligation by EU NCAs and/or the MHRA.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

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

Finding MI.1 b)
The local procedure, [redacted] 'Local Conventions to support Signal Management' [redacted] 30 June 2020), did not provide instructions on the steps to take if a signal requiring escalation was identified outside of authoring the six-monthly signal evaluation report (SER). Global procedure, [redacted] Signal management' [redacted] 13 September 2019), outlined the global signal management process, whereby signal detection activities were captured within an SER. These reports were written at a frequency dependant on the classification of the product (monthly, quarterly or six monthly). All products for which the UK affiliate was responsible had a six-monthly SER associated with them. [redacted] had been written to align with the global procedure and required the UK affiliate to conduct monthly checks of the safety data for designated medical events, important medical events and serious unexpected events. Literature results were also reviewed on a monthly basis for any important safety information. The results of these monthly checks were included in the SER at the time of authoring; however, the SOP did not include any instructions to staff at the UK affiliate on the steps to take if a signal that required escalation was discovered prior to authoring the six-monthly SER. During the inspection, Chiesi stated that an informal process was in place whereby important signals identified on a monthly basis would be discussed with risk management physicians, and an ad-hoc Safety Evaluation Committee meeting could be called. The MAH is reminded of the quality requirements for signal management in GVP IX.B.5 that states "*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*".
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

MI.2 Adherence to procedural timeframes

Finding MI.2 a)
There was a delay of 12 months between deviation supervisor review and quality review (deviation record closure) for two major deviations. The two deviations were raised following the Case Safety Reports Data and Process Quality Check for May 2019 and June 2019, in which ICSRs were identified that required amendments: - [redacted] – Deviation record opened 26 July 2019 and deviation supervisor review conducted on 01 August 2019. However, QA approval did not occur until 06 August 2020, with additional approval received on 13 and 25 August 2020. - [redacted] – Deviation record opened 26 July 2019 and deviation supervisor review conducted on 01 August 2019. However, QA approval did not occur until 06 August 2020, with additional approval received on 06 and 13 August 2020. Section [redacted] 'Management of GVP deviations in TrackWise system' ([redacted] 01 June 2020) required critical and major deviations to be closed within 20 working days from the notification date (date of deviation supervisor review). It is acknowledged that the delay in quality review/closing the deviation records did not impact on the immediate action taken to correct the identified ICSRs in the global safety database, and accordingly this finding has been graded as minor.
Root Cause Analysis
[redacted]

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Further Assessment
[redacted]

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

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Finding MI.2 b)
There was a delay of six months in issuing the non-regulatory compliance monitoring report for the reference period 01 October 2019 - 31 December 2019 (Q4 2019). As per [redacted] 'Global pharmacovigilance system compliance monitoring' [redacted] 30 March 2018), concerned parties were required to update the relevant registers and tools within 15 days from the last day of the analysed quarter, following which the report should be drafted, reviewed, approved and distributed within 30 business days. As per these timelines, the report for Q4 2019 was due on 26 February 2020, however, the report was not approved until 24 August 2020.
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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[redacted]

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

MI.3 Contracts and agreements

Finding MI.3 a)
Section 6 of the agreement between [redacted]. and [redacted] (European subsidiary of [redacted] and subsequently acquired by Chiesi) was entitled 'Anti-Bribery & anti-corruption and audit rights'; however, there was no mention of audit rights within the section. It is acknowledged that Chiesi undertook an audit of [redacted] in November 2019. The agreement was signed in March 2017 (last signature date on 23 March 2017) and covered the conduct of the [redacted] non-interventional category 1 PASS [redacted]
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

C.4.4 Comments

1. Reconciliation of AEs

For [redacted] study [redacted] there had been no reconciliation of AEs between Chiesi and the study contract research organisation, [redacted] since the start of the study (start of data collection was January 2016 according to the protocol) and no reconciliation plan had been drafted.

In light of the recent transfer of the EU marketing authorisation for [redacted] it is recommended that a retrospective reconciliation is conducted to ensure that all relevant AEs have been recorded in the global safety database and reported to EU authorities, as appropriate.

2. Targeted follow-up questionnaires

The [redacted] RMP [redacted] 01 April 2019) required targeted follow-up questionnaires to be sent for adverse reactions concerning the important identified risk 'serious bleeding'. Chiesi had a procedure [redacted] that outlined the RMP requirements for UK authorised products, which accordingly stated that targeted follow-up questionnaires were required for [redacted] However, for non-specific risks, such as 'serious bleeding', the MAH is encouraged to define which specific event PTs meet the requirements for use of a targeted follow-up questionnaire.

3. Coding of adverse events

An isolated example of inaccurate MedDRA coding was identified in an invalid ICSR:

- Case [redacted] Non-serious case from the Netherlands identified in the digital media. The MedDRA LLT 'Vision loss' (which maps to the MedDRA PT 'Blindness') had been coded as an event. However, the source information referred to 'bad vision', for which a more appropriate MedDRA PT would be 'Visual impairment'.

The case was invalid as there was not an identifiable patient, however as the coding of the event may impact signal detection, the MAH is asked to reconsider and update the MedDRA coding in this ICSR.

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

- 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).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Chiesi Farmaceutici S.P.A.	**DATES**	20 - 21 August 2020 02 - 04 September 2020
LOCATION	Remote inspection	**START TIME**	09:00am on all days

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

The scope of the inspection will include the following topics:

- **Signal management**
  - To include signal detection, validation, evaluation and tracking

- **Additional Risk Minimisation Measures (aRMMs)**
  - Implementation of UK educational materials

- **Adverse Drug Reaction (ADR) management**
  - To include:
    - Collection of adverse events from licensing and business partners
    - Submission of ICSRs to EudraVigilance

- **Post-authorisation Safety Studies (PASS)**
  - To include management of safety data and oversight of PASS

Thursday 20 August 2020 – Friday 21 August (Days 1 – 2):

An opening meeting will be held by videoconference on Thursday 20 August at 9.00am (BST), which will be led by the lead inspector. The agenda will be as follows:

- Review of the scope and arrangements for the inspection
- Company presentation by Chiesi to provide an overview of the company, pharmacovigilance system and quality system. The presentation should last no longer than 20 minutes.

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. Please provide a designated contact point who can assist with any ad hoc questions from the inspectors or arrange calls between inspectors and subject matter experts if required.

The following ad hoc calls were held with the listed attendees:

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- *Contractual arrangements with* [redacted]
- [redacted]

Wednesday 02 September 2020 – Friday 04 September 2020 (Days 3 – 4)

Days 3 and 4 of the inspection will be held over three calendar days due to inspector availability.

Remote document review, written requests and ad hoc queries from inspectors where necessary.

A closing meeting will be held via videoconference on Friday 04 September (timing to be confirmed) during which feedback on the inspection will be provided to the company.

The following ad hoc calls were held with the listed attendees:

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- [redacted]
- [redacted]

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

Designated contact point:

[redacted]