Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Celltrion Healthcare Hungary Kft

MHRA Inspection Number: Insp GPvP 34463/18243410-0002

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
NIS	Non-Interventional Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreements
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDEA	Safety Data Exchange Agreement

SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
XEVMPD	eXtended Eudravigilance Medicinal Product Dictionary

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Statutory National Inspection
System inspected:	Celltrion Healthcare Hungary Kft. [redacted]
Site of inspection:	Parexel, The Quays, 101-105 Oxford Rd, Uxbridge UB8 1LZ
Main site contact:	[redacted]
Date(s) of inspection:	Onsite: 03-06 June 2019 Office-based inspection was conducted over 13, 14 and 25 and 26 June 2019
Lead Inspector: **Accompanying Inspector(s):**	[redacted]
Previous inspection date(s):	02-04 June 2016
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):	Argus Safety (8.1.2) (commercially available)
Key service provider(s):	PSUR production and signal detection and management, together with services of the EU QPPV were provided by Parexel. Local UK pharmacovigilance activities were conducted by Napp Pharmaceuticals (see section B.1)
Inspection finding summary:	07 Major findings
Date of first issue of report to MAH:	22 July 2019
Deadline for submission of responses by MAH:	23 August 2019
Date(s) of receipt of responses from MAH:	23 August 2019, 26 September 2019, 17 October 2019
Date of final version of report:	24 October 2019
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Celltrion Healthcare Hungary Kft. 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 (EC) No 726/2004 as amended, Directive 2001/83/EC as amended, Commission Implementing Regulation (EU) No 520/2012 and the adopted good pharmacovigilance practices (GVP) Modules. A list of reference texts is provided at Appendix I.

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The Celltrion group specialises in biosimilars and has three centrally approved (CAP) biosimilar medicines in EU, [redacted] (approved as three brands for different indications under three CAP licences in the EU including [redacted] and [redacted] were authorised in the EU on 17 February 2017 and 08 February 2018 and are therefore subject to additional monitoring. The licences are held by Celltrion Healthcare Hungary Kft., which is a subsidiary of Celltrion Healthcare Co. Ltd., who has delegated all duties relating to pharmacovigilance activities for both companies to Celltrion Inc. (hereafter "Celltrion") through a delegation agreement.

The role of the QPPV is outsourced to Parexel, based in The Netherlands, with a back-up at Parexel located in the UK. Shortly prior to the inspection, Celltrion relocated the PSMF from the UK to The Netherlands. PSUR production and signal detection is also outsourced to Parexel. The management and reporting of ICSRs is performed by the Celltrion Global Safety Data Center Inc. (GSDC) located in the Philippines.

In the UK, Celltrion has established agreements with Mundipharma for import, marketing and pharmacovigilance in the UK. Mundipharma operates on a local level through independent affiliated companies, in the UK this is Napp Pharmaceuticals (Napp). Consequently, UK pharmacovigilance activities are performed by Napp, including the management and implementation of additional risk minimisation measures for [redacted]

B.2 Scope of the inspection

The inspection included a review of the global pharmacovigilance system and was performed at the offices of Parexel in Uxbridge, Greater London. Personnel from Celltrion and Parexel attended the Uxbridge site in order to participate in the inspection. Personnel from Celltrion, Mundipharma and Napp Pharmaceuticals also joined the inspection by web conference and teleconference as required.

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

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (v23.0 dated 15 March 2019) 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.

B.4 Conduct of the inspection

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

The inspection was not completed during the onsite days (03-06 June 2019) and an interim closing meeting was held at the offices of Parexel in Uxbridge on 06 June 2019 to summarise the inspection status and to provide preliminary feedback regarding the inspection findings. The inspection was concluded via office-based document review and interviews were held via teleconference on 14 and 25 June 2019. A formal closing meeting was conducted via teleconference on 17 July 2019.

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

Since the previous inspection in 2016 the company had made the following changes to the pharmacovigilance system:

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- The location of the PSMF was changed from UK to The Netherlands in March 2019.
- The QPPV was changed from [redacted] in March 2019.
- The Celltrion Global Safety Data Center (GSDC) was set up and the management ICSRs was transferred from Parexel to GSDC in early 2019.
- Four licences were approved for [redacted] in the EU via the centrally approved process for varying combinations of indications across oncology and autoimmune disease; [redacted] on 17 February 2017, and [redacted] (previously [redacted] on 13 July 2017. The marketing authorisation (MA) for [redacted] was withdrawn on 12 April 2019 for commercial reasons by Celltrion. Additionally, [redacted] was approved in the EU on 08 February 2018.

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 Ongoing safety evaluation

Requirements:

GVP Module IX.B.2. Signal detection
"Signal detection should follow a methodology which takes into account the nature of data and the characteristics (e.g. time on market, patient exposure, target population) as well as the type of medicinal product concerned"

IX.B.5. Quality requirements
"Signal management is considered a critical process (see GVP Module I). Any signal management system should be clearly documented to ensure that the system functions properly and effectively […] A system of quality management (see GVP Module I) should be applied to all signal management processes"

GVP Module IX Add.I.2 Statistical methods

GVP Chapter PII.B.4. Product- or Population-Specific Considerations II: Biological medicinal products
"Signal detection for biologicals should therefore be specific to the product, as well as the active substance. All steps of signal management should be performed at the level of the product name, as well as the active substance. In case of a signal any effort should be made to identify any common root cause such as batch.

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

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Signal detection was being conducted on a monthly basis for each product by Parexel. The activity included a qualitative review of scientific literature, regulatory alerts and websites, review of any data from clinical trials and ongoing medical review of ICSRs, as well as a quantitative analysis of the electronic Reaction Monitoring Reports (eRMR) from the EudraVigilance Data Analysis System (EVDAS) and of line listings from the safety database. Batch trend analysis (BTA) was only being conducted fo[redacted]

The following deficiencies were identified with regards to signal detection.

Finding	**MA.1 a)**
The specific requirements for biological products described in GVP Chapter P-II (Biological medicinal products), states that processes should be 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*". The following	

deficiencies were identified in the methodology applied for signal detection for Celltrion's biosimilars:

i) There was no mechanism for the notification to the pharmacovigilance department regarding manufacturing changes.

ii) No batch trend analysis had been conducted for two of the EU authorised active substances.

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While it was noted that BTA had been conducted for [redacted] was a review of event counts per preferred term (PT), per batch, for an interval (quarterly and more recently six-monthly). Any single PT with three or more events occurring was highlighted for medical review by the Drug Safety Physician (DSP). Additionally, the DSP would review the reports for any batch in which the total of all events (any PT) received for the interval was 10% or more of the total events from reports that included batch numbers, in accordance with the GSDMP section 4.2.3.3 on p21 (in both v10 and v11).

This approach did not take into consideration reports as they were received cumulatively and therefore did not allow for detection of emerging trends over the entirety of each batch.

iii) The methodology applied to the quantitative review of monthly line listings for each product would not have supported the detection of emerging signals over time. This methodology involved the application of a threshold to the reporting ratio of, the proportion of each event compared with all events received in the interval, to the cumulative reporting proportion for that event, as described in Global Signal Detection and Management Plan (GSDMP) [redacted] section 4.2.1 on p14 in both [redacted] effective 23 July 2018 and superseding [redacted] effective 03 June 2019).

The criteria defined in the GSDMP to identify a potential signal requiring additional review were:

- Total events reported ≥ 3

and

- A reporting ratio ≥ 3

Or

- First time events reported during the review period

Although the thresholds applied to in this signal detection activity would allow for identification of changes to the frequency of reporting, they would not be effective in detecting emerging signals over time, particularly for rarer events, as first set of criteria only triggered a signal for review if an increased frequency of reporting was observed during the reporting period. A method that takes into account comparisons between recent intervals may provide a more sensitive and appropriate approach to detect temporal variations.

GVP Module IX Addendum I.2. 'Statistical methods' describes the detection of changes to ICSR reporting frequency in section I.2.2., but highlights the limitations of this method in that *"results might be less reactive to transient temporal variations since the focus is on changes in statistics based on the cumulative count, not in*

comparing recent counts with the latest count" and recommends the use of "*ongoing quality control measures to ensure acceptable performance*".

It was noted that Celltrion had never detected a signal that was validated for further assessment.

Post inspection request: In the further analysis, Celltrion should consider how the methodology for signal detection can be made more sensitive. Based on the outcome of this, a full review of cumulative data, including batch specific data where applicable, should be conducted with actions taken accordingly.

Root Cause Analysis

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[redacted]

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[redacted]

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Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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[redacted]

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

Finding MA.1 b)

Per Parexel [redacted] Signal Detection and Management', effective 28 February 2018, section 2.10, a List of Terms of Special Interest (LTSI) was reviewed during signal detection. Section 3.2 of the SOP indicated that the terms contained in LTSIs would warrant signal validation on receipt of cases containing these terms.

According to this SOP (section 2.10):

"The baseline LTSI should contain terms listed in the product's RMP (if applicable)"

i) The LTSIs were not in compliant with this procedure in that:

- The LTSI for [redacted] did not include the following 'important potential risks' listed in the RMP (v9.0, 21 November 2017) (indications in brackets):

  - Off-label use in autoimmune disease (rheumatoid arthritis (RA) and granulomatosis with polyangiitis/microscopic polyangiitis (GPA/MPA))
  - Off-label use in paediatric patients (all indications)
  - Relapse of GPA/MPA (GPA/MPA)

  In addition, none of the safety concerns listed in the RMP under 'missing information' were included in the LTSI. These terms included:

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- Use during pregnancy or lactation (all indications),
- Immunogenicity and autoimmune disease (RA and GPA/MPA)
- Longer-term use in GPA/MPA patients (GPA/MPA)

- The LTSI for [redacted] did not include the following safety concerns terms listed under 'missing information' in the RMP (v10.0, 26 February 2019):

  - Safety in very young children (<6 years)
  - Use during lactation
  - Long-term safety in children, children with Crohn's disease and ulcerative colitis and in adults with ulcerative colitis, psoriatic arthritis or psoriasis.

- The LTSI for [redacted] did not include the following safety concerns terms listed under 'missing information' in the RMP (v4.0, 27 September 2018):

  - Treatment in male patients (breast cancer only)
  - Safety of [redacted] dose

ii) As part of the documentation for the signal management process, the LTSIs in use for each product were not compliant with GVP Module IX in that they were not dated or version controlled and managed as part of the quality system

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]

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

MA.2 Quality management for pharmacovigilance

Requirements:

Commission Implementing Regulation (EU) No. 520/2012, Article 8(3)
"The quality system shall be based on all of the following activities: […] (c) quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; (d) quality improvements: correcting and improving the structures and processes where necessary."

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

In October 2018 Celltrion conducted an audit of their service provider Parexel. Two critical observations were reported; one titled 'MAH and QPPV supervision' and the other titled 'ICSR case processing'. Deficiencies concerning visibility of the open CAPA in the PSMF are reported in finding MA.7.

The following deficiencies in the management of non-compliance in the pharmacovigilance system, including from the outcomes of audits, self-identified deviations and CAPA management, were identified:

Finding MA.2

Deficiencies identified and reported from the audit of Parexel in October 2018 had not had a root cause analysis or impact assessment performed prior to agreeing a CAPA plan.

Following this audit, on review of the audit observations including the critical findings, by Celltrion and the EU QPPV (a contractor from Parexel), CAPA records were raised by Celltrion in addition to CAPA proposed by Parexel, to address the deficiencies across both parties.

At the time of the inspection the Celltrion CAPA were ongoing or had been completed in relation to the following areas:

- CAPA metrics and effectiveness
- Quality control of PSURs, alignment of the signal detection and management plan (SDMP) with GVP Module IX Rev 1
- The validation status of the searches used for signal detection and production of

aggregate reports
- Inclusion of clinical trial data held at CROs in signal detection and aggregate reports
- The use of the 'SAE classification' in the database for both cases from investigator initiated studies and non-interventional studies

However, there was no evidence that Celltrion had performed a root cause analysis or impact assessment prior to agreeing the CAPA plans to ensure that the actions would be adequate to address the audit findings.

For example:

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- The CAPA plan documented in record [redacted] outlined an action plan with three possible approaches to remediate the finding that the listings generated for pharmacovigilance purposes were not validated, which was part of the critical finding for 'MAH and QPPV accountability' per PSMF Annex G. Each approach concerned the future extraction of data from the database with a due date of 31 October 2019. Celltrion confirmed that the finding had not been subject to a root cause analysis or investigation into the impact of the issues which had been identified; and as such there was no confidence the line listings which had been generated for regulatory purposes (such as to interrogate the database for data used for aggregate reports or signal detection or evaluation) were accurate.

  A deviation report had additionally recorded the technical deficiencies in an uncontrolled deviation report raised by the service provider who was contracted to extract data from the database, Techsol, which was undated with no reference number. This report did not document any dates when the issues were identified or recorded, and whilst it described corrective and preventative actions, these were limited to Techsol operations only.

Post inspection request: Celltrion should perform an impact analysis on all deficiencies raised through the Parexel audit in October 2018, where Celltrion has raised CAPA records in its quality management system.

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

MA.3 Risk management

Requirements:

GVP Module I.C.1.5. *"The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties […] The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorisation holder"*

GVP Module XVI.B.3. Implementation of risk minimisation measures
"Quality assurance mechanisms should ensure that the distribution systems in place are fit for purpose and auditable"

XVI.B.6. Quality systems of risk minimisation measures
"These records [of RMP update and submission], *the RMP and the associated risk management systems, as well as any documents on risk minimisation measures may be subject to audit or inspection."* [emphasis added]

GVP Module XVI. Add I.2. Principles for educational materials

XVI. Add I.3. Submission of educational materials

A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions. 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. Celltrion had aRMMs in place for two products, [redacted]

The RMP for [redacted] signed 26 February 2019) described in Part V the distribution of educational materials, including a patient reminder card, concerning the more important safety concerns associated with [redacted] treatment, which were provided as part of the product packaging.

Additionally, the [redacted] RMP described that the effectiveness of this tool would be evaluated using the "applied trend analysis tool" to compare relative reported frequencies "actual versus historic". Please refer to finding MA.1 concerning the limitations of the approach that was being applied in practice, and its ability to detect emerging trends.
The RMP for [redacted] signed 21 November 2017) described in Part V the distribution of education materials including:

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- Healthcare professional information document for indications of rheumatoid arthritis and rheumatoid arthritis (RA) and granulomatosis with polyangiitis/microscopic polyangiitis (GPA/MPA) concerning the need to check for contraindications prior to [redacted] treatment and the need for close supervision during product administration, together with detailed information on the risks of infections and progressive multifocal encephalitis (PML) and the need to monitor patients for these
- Patient information document for indications of RA and GPA/MPA, with detailed information on the risks, signs and symptoms of infections and PML
- Patient alert card for the risk of PML for indications of RA and GPA/MPA
- Physician information document for indications of non-Hodgkin lymphoma (NHL) and chronic lymphocytic lymphoma (CLL) to remind the physician that the product should only be administered by IV and to avoid route administration errors

Finding MA.3 a)

The following issues were identified concerning the control and implementation of the educational materials for [redacted]

i) The initial educational materials for [redacted] were submitted to the MHRA on 29 March 2017 for the RA and GPA/MPA indications, which received approval on 10 April 2017, and on 13 April 2017 for the NHL and CLL indications, which received approval on 19 April 2017. However, [redacted] was first launched in the UK on 29 March 2017, prior to the approval of these materials.

ii) The MAH did not submit a detailed implementation plan to the MHRA in line with GVP Module XVI Add I.3. for the distribution of the [redacted] educational materials, which were being made available through the electronic Medicines Compendium (eMC) website; via the medical information service and sales force; and through product packaging (for the patient alert card). Consequently, the dissemination method had not been approved by the MHRA.

iii) The patient reminder card for [redacted] was approved by the MHRA on 06 March 2015, however [redacted] was launched in the UK prior to this, on 25 February 2015.

iv) The version of the patient reminder card that was approved by the MHRA on 06 March 2015 was v1.3 dated 22 October 2014. The version published on the eMC website at the time of the inspection was v2 [redacted] however no evidence of MHRA approval of this version could be provided by Celltrion.

Post inspection request: Celltrion should assess whether the materials being disseminated and published are the MHRA current approved versions. The outcome of this assessment should be provided with the responses to the inspection report. Where there is no evidence to support that these have been approved by the MHRA, the materials should be submitted together with a detailed plan of how the aRMMs are distributed in the UK (as per the guidance in GVP XVI. Add.I.3.) to the MHRA via RMPallocation@mhra.gov.uk for formal review and approval. Records of this should be maintained and may be subject to future inspection in line with GVP XVI.B.6.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

Finding MA.3 b)

Celltrion did not have sufficient oversight and supervision of the additional risk minimisation measures.

i) There were no mechanisms of oversight, by the MAH and the EU QPPV, including of the UK service provider Napp, to ensure that risk minimisation measures were implemented compliantly.

ii) There were no mechanisms for the tracking of the submission and approval of the materials used for additional risk minimisation measures, a process that was conducted on behalf of Celltrion by Napp.

iii) There were no defined timeframes for the recall of outdated educational materials from stakeholders such as medical information or sales staff following the approval of updated versions.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)
[redacted]

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

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[redacted]

Preventative Action(s)
[redacted]

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

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[redacted]

MA.4 Maintenance of authorised product information

Requirements:

Directive 2001/83/EC as amended,
Paragraph 40 *"The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information."*
Article 23(3) *"The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge"*

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 5 Marketing Authorisations, Regulation 76

Commission Implementing Regulation (EU) No 520/2012
Article 11 (1) *"Specific quality system procedures and processes shall be in place in order to ensure the following: […](f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal;"*

When new information about the benefits and risks of a product become available it is often appropriate to make changes to reference safety information documents, such as the summary of product characteristics (SmPC) and patient information leaflet (PIL), so that healthcare professionals and patients are able to use the medicinal product correctly on the basis of full and comprehensive information.

Finding MA.4 a)

Celltrion had failed to ensure that PILs containing updated safety information were being introduced in released batches of product in accordance with the guidance published by the MHRA, which states that, once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months.

https://www.gov.uk/guidance/medicines-packaging-labelling-and-patient-information-leaflets

On 07 July 2016 the EMA requested an update of the PIL for [redacted] Celltrion failed to implement the updated PIL within six months of approval of the safety variation associated with this request.

Five batches of product were released containing the out of date PIL more than six months after the approval of the new PIL was received on 04 October 2016, where the last date that the previous PIL had been released was over a month beyond the deadline on 12 May 2017 (QP Certified date).

Batch Number	Batch Size (Vials)	QP Certified Date
[redacted]	[redacted]	[redacted]

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[redacted]

The information changed in the new PIL included the removal of the wording "in rare cases" in the warnings in section 2 in relation to life-threatening infections including tuberculosis. Section 4 was updated to include "chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, light-headedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, a fast or a slow heartbeat" instead of "changes in your heart beat", and the addition of "temporary loss of sight during or within 2 hours of infusion".

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.4 b)

There was inadequate procedural documentation to describe the update of product safety information following the identification of a new signal, a PRAC recommendation, or to describe the process of comparison of product safety information with reference products. Additionally, there were no defined timeframes to ensure the timely implementation of updated patient information leaflets into product packs.

SOP [redacted] 'Approval of Secondary Packaging Material Mock-up', [redacted] effective 27 July 2017) described a high-level generic process but did not include adequate detail, including what timelines would be applicable.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)

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[redacted]

Preventative Action(s)
[redacted]

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

MA.5 Periodic safety update reports

Requirements:

GVP Module VIII.B.5.6.3. PSUR sub-section "Cumulative and interval summary tabulations from post-marketing data sources"
"Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side." [Emphasis added]

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. At the time of the inspection there was ongoing remediation work regarding the processes to compile data for PSUR production and the quality control (QC) of PSURs. Over the previous seven months, Celltrion had identified and recorded multiple deviations and raised associated CAPA records regarding the quality and accuracy of PSURs. These included PSURs with incorrect worldwide authorisation status and figures, the use of non-validated searches to extract data from the database for the PSUR, inaccuracies in the status of signals included in PSURs, a lack of process to ensure inclusion of relevant data from clinical trials, and ineffective QC missing errors made when authoring PSURs. Additionally, the following deficiencies in PSURs were identified by inspectors:

Finding MA.5
Unrelated adverse events had been included in the cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources in the four PSURs reviewed on inspection. Celltrion confirmed that there was no process to exclude not-related events from inclusion within the PSUR line listings retrieved from the safety database.

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The PSURs reviewed during the inspection were:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

For example, a review of the cumulative line listing used for the [redacted] (DLP 20 January 2018) PSUR included 570 (of [redacted] total events) events which had been assessed as "not related" by the reporter and the company. [redacted] of these unrelated events were from solicited reports (with a case type of 'IIT/NIS or Post Marketing Surv.').

The interval line listing included [redacted] events which had been assessed as not related by the reporter and the company. [redacted] of these unrelated events were from solicited reports.

The inclusion of unrelated events gives an inaccurate presentation of the collected safety information for products during the assessment of a PSUR and has potential to dilute information from reports of related adverse reactions.

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]

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

Comment
The cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources in the reviewed PSURs were not presented as per the recommended template in GVP Module VII (Table VII.8 "Numbers of adverse reactions by preferred term from post-authorisation sources"). The MAH is encouraged to adopt the tabulations illustrated in GVP module VII. Currently the tabulations span over several pages, making it difficult to analyse and interpret all cases received for PT's from different post-marketing sources. Using this tabulation will also remove the need to use the case type "other" which has been included in the [redacted] PSUR (21 January 2016 – 20

January 2017).

MA.6 ICSR management

Requirements:

Directive 2001/83/EC as amended Article 107(3)

GVP Module VI.B.3. *"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."*

The management of ICSRs was transferred from Parexel to the Celltrion Global Safety Data Center (GSDC) in early 2019. The following deficiencies were identified with regards to expedited reporting compliance.

Finding MA.6 a)

Celltrion had not been compliant in expediting ICSRs to EudraVigilance within the timeframes stipulated in Directive 2001/83/EC as amended, Article 107(3).

Between January 2019 – May 2019, monthly compliance reached a maximum of 91% of cases reported on time in May 2019 and a minimum of 78% in March 2019 with an average compliance of less than 86% over the five-month period. It was noted that for the January to December 2018 period, compliance was approximately 95% on average.

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Month	Total submissions	On time	Late	% Compliance
[redacted]				

The decrease in compliance was considered by the company to be related to a case processing backlog (defined by Celltrion as cases on day 10 or above since their initial received date that were still in the case processing workflow). According to figures requested during the inspection, the mean daily backlog of cases between 24 January 2019 and 31 May 2019 was approximately 1800 cases and on occasions reached more than [redacted] cases.

It was stated at interview that Celltrion was aware of the case processing backlog and associated compliance issues and were seeking to mitigate the problem by increasing the numbers of case processing personnel.

Root Cause Analysis

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.6 b)

Celltrion used 'Action Items' in the Argus safety database to track follow-up activity. There were approximately 500 cases where Action Item completion dates were greater than the due dates. Of these 500 cases there were approximately 30 cases where follow-up Action Items had exceeded their due dates by 90 or more days. For example, the following cases had 'Action Code' of "Follow up Query next schedule" and an 'Action Item Description' of "Send query letter again after 14 days":

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Case ID	Action Item Open Date	Action Item Due Date	Action Item Completion Date
[redacted]			

For Action Items not relating to follow-up, there were no documented procedures to describe the administration of action items not related to follow-up activities.

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

MA.7 Pharmacovigilance system master file

Requirements:

Commission Implementing Regulation (EU) No. 520/2012 Article 3(8), Article 4(3) and Article 5(4)

"The marketing authorisation holder shall record in the logbook referred to in point 8 of Article 3 any alteration of the content of the pharmacovigilance system master file made within the last five years, with the exception of the information referred to in point 1(b) to (e) of Article 2 and in Article 3. The marketing authorisation holder shall indicate in the logbook the date, the person responsible for the alteration and, where appropriate, the reason for the alteration."

GVP Module II.B.4.2.
"Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined."

GVP Module II.B.4.7.
"The PSMF shall also contain a note associated with any audit where significant findings are raised […] *in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). […] The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [DIR Art 104(2)]. The addition, amendment or removal of the notes must therefore be recorded in the logbook."*

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Finding MA.7

The PSMF [redacted] approved 15 May 2019) provided to inspectors on day one of the inspection was not compliant with applicable legislation and statutory guidance. Specifically:

i) The PSMF main body did not contain notes associated with significant audit findings, together with the associated corrective and preventative actions. The purpose of including this information in the body of the PSMF is to provide transparency as the addition, amendments or removal of these notes is recorded in the logbook of the PSMF.

Instead, Annex G 'Critical and Major Audit Inspection Findings' included tables of critical and major audit findings, which included the findings from the Celltrion audit of Parexel in October 2018. Information in these tables was not accurate in that the deficiencies which had been assigned to Parexel included a statement that *"Audit Response and CAPA plan being reviewed by the auditee"*. CAPA plans for this audit, relating to both Celltrion actions and Parexel actions, were provided to inspectors during the inspection. Evidence was seen that Parexel had raised CAPA for the findings in their quality management system and completed and closed the CAPA, the majority of which had been closed in April 2019.

ii) In Annex B, 'List of Sites where PV Functions are Undertaken', Napp Pharmaceuticals Ltd. were listed as 'Product Distributor in United Kingdom', this description was not an accurate presentation of their role in the critical pharmacovigilance activity of maintaining and implementing additional risk minimisation measures in the UK, which included the submission of these to the MHRA for approval.

iii) Annex I for v23 of PSMF did not contain all history of changes within the last five years. This history of changes had been included in [redacted]

Post inspection request: The PSMF should be updated to fully reflect <u>all</u> CAPA (together with their status) from the October 2018 audit of Parexel, including those that have been completed. This updated version of the PSMF should be provided to inspectors. Subsequently, any that have been completed may be removed in the next update of the PSMF, with their removal clearly documented in the log book.

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

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 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.

As agreed with Celltrion and documented in the above responses, the following specific CAPA deliverables will be provided to the lead inspector:

- MA.1a: The methodology and outcome of the cumulative signal review of all EU authorised products [due 31 January 2020]
- MA.2: The final impact assessment and root cause analysis for Parexel audit outcomes with associated CAPA actions to address as required [due 31 October 2019]
- MA.6a: Quarterly reports on ICSR backlog management and expedited reporting submission compliance for EU (and UK as required) [up to and including Q4 2020]

Following successful receipt of adequate evidence, the lead inspector recommends that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Directive 2001/83/EC, as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916).
- 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.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Celltrion	**DATE**	03 June 2019
LOCATION	Parexel, The Quays, 101-105 Oxford Rd, Uxbridge UB8 1LZ	**START TIME**	1pm arrival for 1.30pm start

Purpose of Interview	Session Lead	Staff to be interviewed
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system, the quality system and areas undergoing remedial activities *(approx. 20 minutes)*	[redacted]	
Quality management system Including but not limited to pharmacovigilance audits and CAPA management A short presentation should be prepared to describe CAPA (ongoing and completed) in relation to major and critical findings from audits of GSDC and Parexel in 2018.	[redacted]	**Interviewees:** [redacted]
[redacted]		

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MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Celltrion	**DATE**	04 June 2019
LOCATION	Parexel, The Quays, 101-105 Oxford Rd, Uxbridge UB8 1LZ	**START TIME**	9.00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review	-	Inspectors only
Collection, collation and reporting of ICSRs Including the receipt and management of spontaneous and solicited cases.	[redacted]	**Interviewees:** [redacted]

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Ongoing safety evaluation Including: - Monitoring of data in EudraVigilance - Signal detection, assessment, evaluation, prioritisation and tracking	[redacted]	**Interviewees:** [redacted]
LUNCH	-	-
Document review Document review and ad hoc interview sessions as required	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Celltrion	**DATE**	05 June 2019
LOCATION	Parexel, The Quays, 101-105 Oxford Rd, Uxbridge UB8 1LZ	**START TIME**	9.00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Document review	-	Inspectors only
Periodic Safety Update Reports Including scheduling, compilation of source data, authoring and quality control.	[redacted]	**Interviewees:** [redacted]
Maintenance of reference safety information - Identification of required updates from various sources - Submission of safety variations - Implementation of approved updates to product information including IB, SmPC, patient information leaflets and online sources of information	[redacted]	**Interviewees:** [redacted]
LUNCH	-	-

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Risk management Including but not limited to: - Implementation of UK additional risk minimisation measures - Oversight and compliance management of risk management plan commitments	[redacted]	**Interviewees:** [redacted]
Document review	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Celltrion	**DATE**	06 June 2019
LOCATION	Parexel, The Quays, 101-105 Oxford Rd, Uxbridge UB8 1LZ	**START TIME**	9.00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Oversight and supervision of the pharmacovigilance system by the MAH and by the QPPV	[redacted]	**Interviewees:** [redacted]
LUNCH	-	-
Document review and ad hoc interview sessions as required	-	Inspectors only
Inspectors meeting	-	Inspectors only
Closing meeting	-	All welcome

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