Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Genethics Group

MHRA Inspection Number: Insp GPvP 36174/19108996-0001

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Centrally Authorised Product
CAPA	Corrective and Preventative Action
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CSR	Clinical Study Report
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HCP	Healthcare Professional
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
NIS	Non-Interventional Study
PAES	Post-Authorisation Efficacy 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(s) inspected:	Genethics Europe Limited [redacted] Activase Healthcare Limited [redacted] Chelonia Healthcare Limited [redacted] All three Pharmacovigilance System Master File Location codes above referred to the same pharmacovigilance system described in a single PSMF.
Site(s) of inspection:	Remote inspection, performed at 10 South Colonnade, Canary Wharf, London E14 4PU.
Main site contact:	[redacted] Třtinová 260/1 Prague 9, 196 00, Czech Republic [redacted]
Date(s) of inspection:	Remote inspection conducted 26th – 28th November 2019
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	N/A
Purpose of inspection:	To review the maintenance of reference safety information (RSI).
Products selected to provide system examples:	All products were subject to review during the inspection.
Name and location of EU QPPV:	[redacted] Contact details as above
Key service provider(s):	Not applicable
Inspection finding summary:	1 Critical finding 1 Major finding 1 Minor finding
Date of first issue of report to MAH:	20th January 2020
Deadline for submission of responses by MAH:	25th February 2020
Date(s) of receipt of responses from MAH:	24th February 2020
Date of final version of report:	24th March 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Genethics Group (hereafter "Genethics") 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 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.

Genethics is a pharmaceutical company headquartered in the United Kingdom, focussed on generic prescription medicines and were selected for inspection as a result of the MHRAs risk based inspection process. Genethics held UK marketing authorisations (MA) under three MAHs: Chelonia Healthcare Ltd, Activase Healthcare Ltd and Genethics Europe Ltd. The pharmacovigilance teams at Genethics were based in Czech Republic, and Mumbai and Hyderabad in India. The European Regulatory Affairs team were based in London.

B.2 Scope of the inspection

The inspection was focussed on the maintenance of the safety sections of the MAH's authorised product information for UK authorised products. The inspection was performed remotely, with the inspection team based at MHRA's headquarters in Canary Wharf, London. Personnel from Genethics were available via teleconference throughout the inspection.

The inspection was performed using interviews and document review. The Inspection Plan (attached as Appendix II) outlines the scope of the review.

B.3 Documents submitted prior to the inspection

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The company submitted a PSMF ([redacted] effective 07-Oct-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.

A closing meeting was held remotely to review the inspection findings on Thursday 28th November. A post-inspection letter was sent to Genethics on 5th December informing them of an upgrade of finding CR.1 from a major to a critical grading, and to request further information regarding the batches released for products [redacted] n relation to the finding described in MA.1.

A list of the personnel who were present during interview sessions are available in records which will be archived together with the inspection notes, a list of the documents requested during the inspection, the inspection report and post-inspection letters and responses.

SECTION C: INSPECTION FINDINGS

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

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

C.2 Definitions of inspection finding gradings

Critical (CR): a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major (MA): a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor (MI): a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Comment: the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

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

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

CR.1 Safety Communication

Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions, minimising risks and contributing to the protection of patients' and public health.

As the regulator of the pharmaceutical industry in the UK, the MHRA does instruct MAHs to update product information in line with current scientific knowledge. Where these updates are assessed as having the potential to impact upon prescribing practices, and reduce the risks of patients taking medicines, instructions and deadlines are given to ensure a consistent message is delivered to patients and healthcare professionals.

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In July 2016, the MHRA contacted all MAHs of [redacted] licences in the UK to mandate an update to the product information, including optimised posology for paediatric patients. MAHs were given until the 30th September 2016 to submit variations to make the changes to the SmPC and PIL and were instructed *"to start incorporating the new dosage information into packs at the next production run and by 31st December 2016 at the latest. Batches released to the market after this date must be issued with product information including the revised posology."*.

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

Finding CR.1 a)

The MAH had failed to implement the updated PIL in packs in line with MHRA instructions following a change to the posology of [redacted] or paediatric patients.

During the inspection documentation for [redacted] was reviewed. This licence was a General Sales List (GSL) licence, meaning there was no prescription or conversation with a healthcare professional required prior to purchasing. Included in the licence documentation were mock-ups for two supermarkets, for which the MAH had own-label supply agreements.

The MAH had submitted the variation in line with the MHRA deadline and this was approved

on the 28th October 2016. The changes in paediatric posology from the previous version of the PIL (CL2) to the newly approved PIL (CL3) are outlined below.

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[redacted]

The previous [redacted] was packed into batches and certified for release by the Qualified Person (QP) up until 24th July 2017 (final batch packed with [redacted] was [redacted], seven months after the deadline imposed by the MHRA. In total, the MAH confirmed that 35 batches had been QP certified with the [redacted] after the 31st December 2016 deadline; which equated to [redacted] packs being released to the market without the changes to the paediatric dosing included within them.

All product had expired at the time of the inspection, so no immediate actions were required of the MAH. However, a critical grading was issued because the dosing change for children aged between 10-15 years had been halved, which represented a significant update to ensure safe use of the medicine; parents / guardians buying this product for children would have been reliant on the dosing instructions included within the leaflet due to its GSL classification.

Root Cause Analysis

[redacted]

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Further Assessment

[redacted]

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[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]	

C.4.2 Major findings

MA.1 Reference Safety 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 including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004."*

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Finding MA.1 a)

The MAH had failed to identify changes required to product information contained within Periodic Safety Update Single Assessment (PSUSA) reports published on the EMA website.

i) The PSUSA report for [redacted], position adopted in the December 2017 CMDh meeting, included within Annex II required changes to the product information as a result of the assessment. These changes included updates to section 4.8 of the SmPC and to the PIL, including additions and clarifications regarding the potential side effect of anaphylaxis. The implementation date included in the assessment report for MAHs to submit variations was the 28th March 2018.

ii) The PSUSA report for [redacted], position adopted in the April 2018 CMDh meeting, included changes to the product information required as a result of the assessment. These changes to the SmPC and PIL included warnings about the impact [redacted] may have on [redacted] if taken concomitantly. The implementation date included in the assessment report for MAHs to submit variations was the 8th August 2018.

iii) The PSUSA report for [redacted] position adopted in the October 2018 CMDh meeting, included changes in dosing for elderly patients within the SmPC. The implementation date included in the assessment report for MAHs to submit variations was the 30th January 2019.

Genethics confirmed none of these changes had been identified or implemented into the product information.

When a PSUR single assessment procedure leads to a variation of marketing authorisations, MAHs for nationally authorised products containing the active substance(s) concerned should submit a variation to align their marketing authorisation with the single assessment outcome, even if their product was not in the direct scope of the procedure (such as a generic medicine or a medicine authorised on the basis of well-established use).

Post-inspection, Genethics was instructed to submit the variations and gave confirmation that the changes would be implemented within packs three weeks after the approval of variations. The company was also informed that batch-specific variations were required for any batches of the above products planned for release with the previous versions of the PILs.

Root Cause Analysis

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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[redacted]

[redacted]	

Preventative Action(s)

[redacted]

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

Finding MA.1 b)

Poor quality variations had been submitted to the MHRA:

i) A [redacted] variation was submitted for [redacted] on 12th December 2017 to update the SmPC section 4.4 and 4.8 and the respective PIL section with the PRAC recommended wording on the risk of acute generalised exanthematous pustulosis (AGEP) with [redacted] The deadline of two months was written in the published minutes on 23rd October 2017. The submission was refused as the MAH had failed to submit the updated clean PIL text with the variation. The variation was re-submitted on 22nd December 2017 and approved on 05th January 2018. At the time of the PRAC update the product was not marketed in the UK.

ii) A grouped [redacted] variation was submitted for [redacted] on 11th July 2019 to update SmPC section 4.8 and the respective PIL section with the PRAC recommended wording on maculopathy with [redacted] The deadline of two months was published in the minutes on 11th June 2019. The submission was refused as the submitted PIL text was not updated verbatim in line with the PRAC wording. The variation was re-submitted on 15th August 2019 but was refused again as the PIL text still did not include the exact PRAC wording. A third variation was submitted on 21st August 2019 and approved on 6th September 2019. At the time of the PRAC update both products were not marketed in the UK.

This sub-finding is considered minor in nature but has been grouped with the major finding. It is important that submissions are of high-quality to ensure that MHRA assessment and review time is not wasted.

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

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[redacted]

C.4.3 Minor findings

MI.1 Provision of Information to Regulatory Authorities

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Finding MI.1 a)
PSMF [redacted] dated 7th October 2019 was submitted to the MHRA prior to the inspection to aid in inspection planning. [redacted] "Safety Variations" made reference to Annex H3, which was a list of company products subject to any Article 31 referrals. This Annex wasn't submitted to the Agency with the PSMF and had to be requested during the inspection.
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)

There were examples identified where Genethics had not informed the MHRA of changes of marketing status of UK authorised products:

i) [redacted] MHRA was notified on 11 November 2019 with a delay of 12 months that the products were not marketed effective 01 November 2018 and 02 November 2018, respectively.

ii) [redacted] MHRA was notified on 08 April 2019 with a delay of eight months that the product was not marketed effective 03 August 2018.

Under regulation 73(3) of The Human Medicines Regulations 2012 as amended, the holder of a UK marketing authorisation must notify the licensing authority if the product to which the authorisation relates is to be withdrawn from the market in the United Kingdom (whether temporarily or permanently). This notification must be given before the beginning of the period of two months ending with the date on which the product is to be withdrawn from the market (unless it is not reasonably practicable to do so, in which case it must be given as far as is reasonably practicable in advance of the date on which the product is withdrawn from the market).

iii) [redacted] The product was marketed from April to July 2018; however, this was not communicated to the MHRA. Under regulation 73(1) of The Human Medicines Regulations 2012 as amended, the holder of a UK marketing authorisation must notify the licensing authority of the date on which the product to which the authorisation relates is placed on the market in the United Kingdom.

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]	

C.4.4 Comments

i) When submitting a safety variation which includes the implementation of wording required as per the QRD product information template, Genethics should ensure that the relevant changes in line with the QRD template are applied throughout the SmPC and PIL.

As an example, a [redacted] variation was submitted for [redacted] on 20 July 2018 to update the SmPC in line with the originator product and the QRD template. However, it was noted that the wording in SmPC section 4.8 and PIL section 4 on the reporting of adverse reactions to the MHRA was not updated to include "or search for MHRA Yellow Card in the Google Play or Apple App Store" as per QRD template Appendix V Adverse drug reaction reporting details.

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

Given the seriousness of the inspection findings, the Inspection Action Group for GCP and Pharmacovigilance (IAG) has recommended that the next MHRA pharmacovigilance inspection is performed within the next 18 months, to review the impact of the actions taken in response to the inspection findings. Please note that this inspection may be conducted unannounced or at short notice.

APPENDIX I REFERENCE TEXTS

- 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).

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC		
PHARMACOVIGILANCE INSPECTION OF	Chelonia	**DATES**	26 – 28 November 2019
LOCATION	Remote inspection	**START TIME**	09:00 GMT (10:00 CET) each day

Inspection plan

This inspection will be focused on the maintenance of reference safety information. To assist in scheduling availability of personnel some interview sessions have been outlined below.

Day 1

There will be an opening meeting at 09:00 GMT (10:00 CET) to review the scope of the inspection. Chelonia are asked to lead a company presentation which aims to orientate the inspectors around the company, the pharmacovigilance system and the quality system. This presentation should last no longer than 20 minutes.

An interview session will occur at 13:00 GMT (14:00 CET) regarding the pre-submission processes, including but not limited to identifying potential changes and timeframes for submission.

Day 2

There will be an interview scheduled at 10:00 GMT (11:00 CET) regarding the post-approval processes, including but not limited to, the control of updating PILs into packs.

Day 3

There will be a closing meeting scheduled for the afternoon, a definitive time will be agreed during the morning.

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

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[redacted]