Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Accord Healthcare Ltd

MHRA Inspection Number: Insp GPvP 20075/309698-0007

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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
CMO	Contract Manufacture Organisation
DCP	Decentralised Procedure
DHPC	Direct Healthcare Professional Communication
DMRC	Defective Medicines Reporting Centre
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAP	Nationally Authorised Product
NCA	National Competent Authority
PIL	Patient Information Leaflet
PIQ	Patient Information Quality Unit
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
QP	Qualified Person

QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SAE	Serious Adverse Event
SDEA	Safety Data Exchange Agreement
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

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Inspection type:	Re-inspection
System(s) inspected:	Accord Healthcare SLU, PSMF MFL2508
Site(s) of inspection:	Accord Healthcare Ltd Sage House 319 Pinner Road Harrow, HA1 4HF
Main site contact:	[redacted]
Date(s) of inspection:	27 January 2020 remote inspection 28-29 January 2020 on-site inspection
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	19-23 November 2018 20-23 May 2014 20-23 September 2011 15-17 September 2010 23-24 September 2009
Purpose of inspection:	Re-inspection to determine if appropriate action had been taken from the previous inspection and 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):	PVEdge (bespoke system)
Key service provider(s):	Pharmacovigilance services provided by Lambda Therapeutic Research Ltd. Medical information services provided for UK and Ireland by Accord-UK Ltd and by Lambda for the rest of the EU. Regulatory affairs activities for some UK products were conducted by Accord-UK Ltd.
Inspection finding summary:	03 Major findings 01 Minor finding
Date of first issue of report to MAH:	03 March 2020
Deadline for submission of responses by MAH:	06 April 2020
Date(s) of receipt of responses from MAH:	06 May 2020, within agreed extension 27 May 2020
Date of final version of report:	09 June 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Accord Healthcare Ltd was selected for re-inspection as a result of the critical finding that was identified during the previous routine inspection of the MAH, performed on 19-23 November 2018. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the previous inspection. In addition, the inspection provided an opportunity to re-examine the overall compliance of aspects of the pharmacovigilance system 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 practice (GVP) Modules.

A list of reference texts is provided at Appendix I.

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Accord Healthcare Ltd has over 600 marketing authorisations in the UK, the majority of which are generic medicines licenced through national, decentralised and mutual recognition procedures, with 29 products centrally authorised in the EU. Most marketing authorisations covered by this pharmacovigilance system are held by Accord Healthcare Ltd, with others under the company names of Accord-UK Ltd and Galenicum Health SL. The pharmacovigilance system is described in [redacted] which is located in Poland.

Accord Healthcare Ltd is part of Intas Pharmaceuticals Ltd, a global pharmaceutical organisation. Accord-UK Ltd is a UK affiliate of Accord Healthcare Ltd, and operates a separate pharmacovigilance system for a UK only portfolio of products; comprising licences held by Accord-UK Ltd and Accord Healthcare Ltd. This system is described in PSMF [redacted] which is linked to PSMF [redacted] The Accord group maintain the separate pharmacovigilance systems as future preparedness following the UK's departure from the EU.

Most pharmacovigilance activities for the Accord Healthcare SLU pharmacovigilance system [redacted]) are outsourced to service provider Lambda Therapeutic Research Ltd, with some local pharmacovigilance activities including UK medical information, outsourced to Accord-UK Ltd.

Regulatory affairs activities for the products covered by the pharmacovigilance system described by [redacted] are conducted by Accord Healthcare Ltd and Accord-UK Ltd. Around 80% of licences fall within the remit of the Accord Healthcare regulatory affairs team and the remaining 20% are conducted by the Accord-UK regulatory affairs team and are subject to the processes in place under [redacted] as there is a separate quality management system in place.

B.2 Scope of the inspection

The inspection focussed on a review of the systems and processes which were associated with the critical finding identified during the previous inspection, in particular the global and UK processes for maintaining product safety information. The inspection was performed at Accord Healthcare Ltd's offices in Harrow, London and personnel from Accord Healthcare Ltd, Accord-UK Ltd and Lambda Therapeutic Research Ltd attended the site in order to participate in the inspection. On 28 and 29 January 2020, the Accord Healthcare Ltd Harrow site was also subject to an MHRA GMP inspection (Insp GMP/GDP/IMP 20075/2813978-0005), which was conducted in parallel to this pharmacovigilance re-inspection.

The inspection was performed using interviews and document review (including records from batch certification). 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

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The company submitted a PSMF [redacted] to assist with inspection planning and preparation. Specific additional documents including deliverables from the corrective and preventative actions associated with the critical finding reported from the 2018 MHRA GPvP inspection were also requested by the inspection team and provided by the company prior to the inspection.

A teleconference was requested by the company prior to the inspection which took place on 22 January 2020. During this call, the company provided information about deviations recently identified within the pharmacovigilance system (please refer to section C.4.1.), and associated deviation records were provided after the call.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. The inspection included a scheduled office-based inspection day, which was held on 27 January 2020, to review documents provided in response to document request sheet A.

A closing meeting was held to review the inspection findings at Sage House in Harrow on 30 January 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

Since the previous inspection in 2018 the company had made the following changes to the pharmacovigilance system:

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- The role of the QPPV remained at the service provider Lambda, however had transferred from [redacted] based in Poland.
- The Accord group had established a new Scientific Affairs function into which both pharmacovigilance systems were reporting.
- Actions taken since the last inspection are described in section C.4.1.

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

A critical finding was reported from the MHRA GPvP inspection of Accord Healthcare Ltd in November 2018 (Insp GPvP 20075/309698-0006), for failures in keeping product information up to date. Accord Healthcare Ltd had failed to ensure that patient information leaflets (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.

During this re-inspection, the systems in place to ensure timely introduction of updated leaflets into packaging and timely availability of updates to approved product information were reviewed in detail. The critical deficiency identified during the previous inspection had been partially addressed and was no longer considered to be a critical finding, although there were still activities ongoing to resolve deficiencies relating to this matter. A separate major finding (MA.1) has been raised in relation to the submission and management of safety variations in the maintenance of reference safety information. In addition, deficiencies in the implementation of specific aspects of CAPA have been raised in finding MA.2.

As part of the corrective actions to the 2018 inspection, Accord committed to conducting a six-month review of the of the implementation of new measures introduced to ensure timely introduction of updated PILs into product packs. During this review, two deviations were identified in relation to the implementation of approved updates to patient information leaflets. These were recorded and notified to the Lead Inspector shortly prior to the re-inspection. Although these deviations were self-identified, they have been included in this report to ensure delivery of the associated CAPA plans and provide assurance of the complete resolution of the critical deficiency observed in 2018.

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Deviation 1 [redacted] dated 16 January 2020):
Where Type [redacted] variations had been submitted to update product information following the publishing of approved wording by the PRAC, Accord had not been implementing the changes immediately and instead mistakenly awaited approval from authorities for these variations before starting the implementation timeframe to introduce PILs into product packs within a six-month deadline.

- Whilst most of the affected products were subject to less than three months delay, there were five batches of [redacted] that were identified to have been certified between five and a half to seven months beyond the six-month deadline to implement significant safety changes to the PIL.

  After the inspection, due to the length of the delay and nature of changes, following assessment by the MHRA's Defective Medicines Reporting Centre (DMRC) and Patient Information Quality unit (PIQ), a Class 4 drug alert was issued on 12 February 2020 and any certified but unreleased stock was to be repacked.

- A total of 25 unreleased batches of other products were identified to contain leaflets that were outdated by less than one month (based on the 6-month deadline to implement a new version) but had not yet been certified. Accord planned to submit Type II batch specific variations (BSVs) for these including 24 batches of [redacted] products which were missing a significant warning regarding [redacted]

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Deviation 2 [redacted], dated 21 January 2020):
Since the November 2018 inspection responses, six further batches of four products were certified beyond the six-month cut-off to implement PIL updates. Most of these were between five and 13 days over the deadline, however one batch was beyond 66 days. The root cause to the deviation was stated to be due to a check on the artwork in the batches having occurred prior to QP certification, and a reliance by the QPs on this check during certification.

The proposed actions to resolve the self-identified deviations were included within the scope of this inspection. In discussions of these deviations with inspectors, Accord have committed to introduce a real-time check of the artwork version during QP certification to ensure compliance with the marketing authorisation. Additionally, Accord Healthcare Ltd will conduct a monthly check on the compliance of timely PIL introduction.

Successful implementation of these proposals should provide robust mechanisms to ensure that the correct leaflet is used in batches at the time of QP certification to provide patients and healthcare professionals with up-to-date safety information.

Deviation 1	
The MAH should provide the final CAPA plan to deviation [redacted] to confirm the commitment to fully addressing the partially resolved critical finding from 2018.	
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]

Deviation 2
The MAH should provide the final CAPA plan to this deviation [redacted] to confirm the commitment to fully addressing the partially resolved critical finding from 2018.
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)

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C.4.2 Major findings

MA.1 Maintenance of RSI

Requirements:

Directive 2001/83/EC as amended Article 23(3) *"The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge"*

Regulation (EC) No. 726/2004 as amended, Article 16(3)

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

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Two regulatory affairs departments were conducting the submission of safety variations for the products covered in the Accord Healthcare SLU PSMF [redacted], the Accord Healthcare Ltd regulatory affairs department and the Accord-UK Ltd regulatory affairs department.

With the exception of the example in finding MA.1a), the examples reviewed by inspectors, from both regulatory affairs departments, demonstrated timely initial submission of safety variations. However, undue delays to variation approval were caused by poor quality submissions with examples of failures to respond to rejected submissions (MA.1b) or requests for further information (RFI) received from the MHRA (MA.1c).

Finding MA.1 a)

Accord Healthcare Ltd had failed to submit a safety variation following a PRAC signal for [redacted] and interstitial lung disease [redacted] for the update to the product information which included the following update to the PIL:

"4. Possible side effects
Rare side effects (may affect up to 1 in 1000 people)
[…]
Coughing, wheezing and shortness of breath which may be accompanied by a high temperature"

The signal was first published on 01 October 2018 with a deadline to submit a variation within two months (over a year prior to the inspection). Accord confirmed that Type [redacted] variations had been submitted to other relevant member states in the procedure, however the MHRA were inadvertently missed from these submissions.

The updated PIL including this update (version as yet unnotified to the MHRA) was issued in artwork database by Accord on 05 July 2019, but no batches had yet been released with new PIL. The last batch of [redacted] was certified on 06 August 2019 and contained the previous version of the PIL.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]
Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)

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[redacted]

Finding MA.1 b)

Accord Healthcare Ltd had failed to respond in a timely fashion to submissions that had been rejected due to errors made when submitting variations. This embedded undue delays to updating product information.

- A [redacted] variation was submitted on 08 August 2019 in relation to [redacted] following a PRAC recommendation to add a warning on maculopathy to section 4.8 of the SmPC (published 11 June 2019). The variation was refused as the submitted dossier only contained a text version of the PIL and a non-acceptance of notification letter was sent by the MHRA accordingly on 28 August 2019. This variation had not been resubmitted at the time of the inspection, five months later.

- A [redacted] variation was submitted on 02 January 2019 in relation to [redacted] to add warnings regarding a potential interaction with [redacted] o section 4.5 of the SmPC and the addition of hyponatraemia to section 4.9 (published 05 November 2018). The variation was rejected as it was not made in the mandatory eCTD format and a rejection notice was sent accordingly on 23 January 2019. Resubmission of this variation did not occur until 28 June 2019, five months after rejection.

- A [redacted] variation was submitted on 04 January 2019 in relation to [redacted] following a reference product comparison (conducted in September 2018) to add further warnings on respiratory depression, hypothrombinaemia and seizures to section 4.9 of the SmPC. The variation was rejected as it was not made in the mandatory eCTD format and a rejection notice was sent accordingly on 09 January 2019. The variation was resubmitted over 10 months later on 22 November 2019.

- A [redacted] variation was submitted on 03 July 2019 in relation to [redacted] following a PRAC recommendation to strengthen the warnings around use in pregnancy to section 4.6 of the SmPC (published 08 April 2019). The variation was refused by the RMS (the Netherlands) on 15 July 2019 due to incorrect variation categorisation. A subsequent variation was not submitted until 06 September 2019, nearly two months after variation refusal.

During the inspection, the MAH confirmed that there was no formal procedure for resubmission of rejected variations, and that normally all resubmissions were being conducted after completion of planned variations. Resubmission of variations was not accounted for in the MAH's variation compliance metrics.

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]	

Finding MA.1 c)
Accord Healthcare Ltd had failed to respond in a timely fashion to requests for further information (RFI) due to errors made when submitting variations causing undue delays to updating product information. • A [redacted] variation was submitted on 28 December 2018 in relation to [redacted] following a PRAC recommendation (published 01 October 2018) to add warnings on aortic aneurysm to section 4.4 of the SmPC and section 2 of the PIL.

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The variation was submitted by the required deadline however, after some correspondence with the MHRA, a response to the RFI requested by the MHRA on 01 May 2019 was not received until over six months later on 07 November 2019.

- A [redacted] variation was submitted on 31 January 2019 to update section 4.2 and 4.5 of the [redacted] SmPC following a reference product comparison exercise conducted in October 2018. The update included the addition of instructions relating to the prescription of the most appropriate pharmaceutical form and strength according to age, weight and dose, and a potential drug interaction with [redacted]

  The variation was invalidated as the MAH failed to respond to a validation correction request sent by the MHRA on 14 February 2019. No variation has since been resubmitted, and the variation was incorrectly recorded as 'under assessment' on the variations tracker.

N.B. These examples were managed by the Accord Healthcare Ltd regulatory affairs team and the receipt of RFI was only tracked for variations managed by the Accord-UK Ltd regulatory affairs team. Responses should consider both processes and whether there are variations currently with pending RFI.

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.2 Implementation of corrective and preventative action plans

Requirements:

GVP Module III (Rev 1), III.C.5. Role of marketing authorisation holders and applicants
"[…] *to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.*"

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The review of the CAPA from the 2018 inspection revealed that the post inspection investigations and CAPA had not been applied to all aspects of the pharmacovigilance system described in [redacted]

Finding MA.2 a)

In the November 2018 MHRA GPvP inspection of Accord Healthcare Ltd, finding MI.4 cited delays in uploading product information to the UK electronic Medicines Compendium (eMC) website, which was used at the time as the source of current product information by internal staff at the MAH.
A deficiency was identified in relation to the corrective actions to this finding which involved the review of product information published on the eMC website. This action was:

"Verification of the eMC database for the availability of the latest SmPC and PIL for all Accord Healthcare Limited UK portfolio"

However, the check that was conducted did not verify that the published documented were the latest versions. In addition, only products managed by the Accord Healthcare Ltd regulatory affairs team were included in this review.

The products included in this check of eMC numbered only 526, whereas Annex H.1 of PSMF [redacted] lists 605 authorised UK products on the 'Annex H.1 List of products covered by the PV' MS Excel sheet and 161 authorised UK products on the 'Annex H.1 List of products covered by the PV - COO' MS Excel sheet.

Two examples of product information updates for products managed by Accord-UK Ltd were selected for review by inspectors, and one of these had not been updated on the eMC website. Updates to the [redacted] product information were approved on 22 January 2019, which included updates to the SmPC to section 4.4 'Special warnings and precautions for use' and multiple updates to section 4.8 'Undesirable effects', with one such warning including:

[redacted] *is not recommended during the first trimester of pregnancy and in women of childbearing potential not using contraception"*

The updated product information was uploaded to the eMC website during the inspection on 29 January 2020. Importantly, the Accord UK website (https://www.accord-healthcare.com/uk/products/actavis-legacy-products) directly linked to product information published on eMC for Accord-UK Ltd managed products including those covered by the pharmacovigilance system described in [redacted]

Root Cause Analysis

[redacted]

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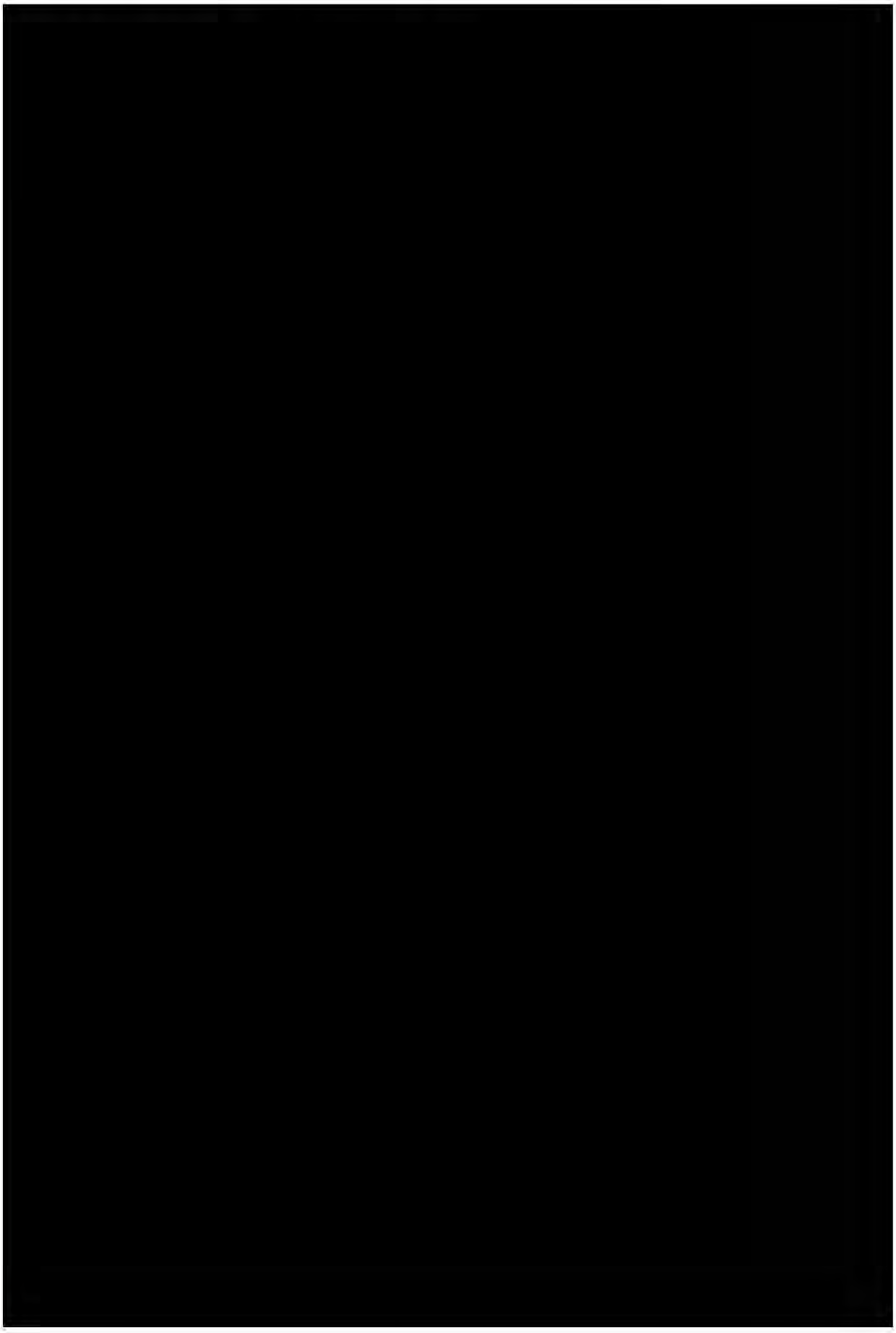

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Further Assessment
[redacted]

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]	

Finding MA.2 b)
In response to the 2018 critical finding, Accord Healthcare Ltd committed to putting controls in place to prevent the use of old artwork in packaging. To ensure the effective implementation of these controls at contract manufacturing organisations (CMOs), Accord Healthcare Ltd also committed to conducting a desktop audit of the inventory system controls used at CMOs. The desktop audit conducted consisted only of a questionnaire sent to the 21 current CMOs, no additional evidence was requested as part of the audit. The written responses were collated including responses to questions such as:

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"What mechanism the artworks are managed within your system? Is it ERP system module or manual system?".

In the responses from Intas Pharmaceuticals Limited (Biopharma Division), the responder stated *"Manual system is available"*, with reference to an SOP [redacted] however no further evidence, including this SOP was requested.

A total of eight responders stated that manual systems were in use compared with 13 that used electronic systems. In contrast, information provided to the inspectorate (in the responses to the 2018 GPvP inspection report and in the letter provided to IAG dated 07 January 2020) confirmed that 20 of the CMOs did in fact use electronic systems, including Intas Pharmaceuticals Limited (Biopharma Division), as confirmed by Intas Pharmaceuticals Limited (Biopharma Division) SOP [redacted] 'Artwork Management' [redacted] Despite the discrepant information, no further confirmatory action was taken following the desktop audit.

Accord should verify that the information provided to IAG was accurate in view of the responses to the audit questionnaire and should consider a more robust approach to fulfilling this CAPA commitment.

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.3 Pharmacovigilance system master file

Requirements:

Commission Implementing Regulation (EU) No. 520/2012, Article 2(4)(e)

GVP Module II.B.4.5. PSMF section on pharmacovigilance processes
A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects shall be included in the PSMF: […]Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications"

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Finding MA.3

The activities relating to the products listed in Annex H of [redacted] are conducted by Accord Healthcare Ltd. with certain pharmacovigilance activities outsourced to Lambda Therapeutic Research Ltd and Accord-UK Ltd. In addition, regulatory affairs activities were conducted by Accord-UK Ltd on behalf of Accord Healthcare Ltd for certain products listed in Annex H of [redacted]

Section 5.2.6 'Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets' of [redacted] dated 10 January 2020, stated that:

"All requests related to safety variations are logged in a tracker along with the due date of submission. The request for variation application (if required) is initiated through change control form by the concerned department within the MAH."

It was confirmed during the inspection through interview and review of SOPs from both organisations that the two regulatory affairs teams operated different processes for this activity for products covered by [redacted] The process at Accord-UK Ltd was not described in the PSMF and did not involve the use of change control to initiate the variation process.

The PSMF impeded inspectors' abilities to review the systems in place and did not fulfil the requirements of the Commission Implementing Regulation (EU) No. 520/2012, which states in paragraph 3 that the PSMF should enable national competent authorities to verify compliance concerning all aspects of the pharmacovigilance system.

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

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

C.4.3 Minor findings

MI.1 Data integrity

Finding	**MI.1**
Pre-inspection document request A8 was for *"an Excel listing of safety variations relating to UK SmPC changes submitted since January 2018".* Entries concerning the delayed introduction of updated PILs into packaging that were recorded in deviation [redacted] were missing from the response provided to request A8 or were incorrectly presented. Specifically, only one of the four products in the deviation was presented accurately in the data, with the following errors for the other three products: • The variation for [redacted] (updates to SmPC sections 4.3, 4.4 and 4.5 and PIL section 2) approved 02 April 2019 following PSUR assessment was not included. • The last batch of [redacted] with the old PIL version was QP certified on 03 April 2019 (after the internal cut-off date of 26 March 2019), however this was incorrectly presented in the listing of variations as QP certification date of 04 March 2019. • The last batch of [redacted] with the old PIL was certified on 10 May 2019, over 6 months after the variation approval, however in the listing of variations there was no date listed for last batch certified with the old PIL, which instead stated "N/A".
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]	

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

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

APPENDIX I REFERENCE TEXTS

- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended
- Directive 2001/83/EC, as amended
- Commission Implementing Regulation (EU) No 520/2012
- Guideline on good pharmacovigilance practices (GVP)
- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916)

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

Medicines & Healthcare products Regulatory Agency

Confidential Information

MHRA Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Accord Healthcare Ltd	**DATE**	27 January 2020
LOCATION	REMOTE INSPECTION DAY	**START TIME**	9:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Day one of the inspection will be conducted remotely through document review by inspectors. A formal opening meeting will be held on site on day 2 of the GPvP inspection.		[redacted]

N.B.
Relevant SOPs, working practices, training records, CVs and job descriptions should be available to the inspection team as requested.
Other documents will be requested during the inspection.
The inspection plan may need to be amended during the inspection.

AA: Anna Adams, BW: Beth Webb

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PHARMACOVIGILANCE INSPECTION PLAN

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MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Accord Healthcare Ltd	**DATE**	28 January 2020
LOCATION	Sage House, 319 Pinner Road, Harrow, HA1 4HF	**START TIME**	10:00

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 and the implementation of CAPA following the critical finding from the 2018 GPvP inspection. Please include any ongoing remedial work ongoing in this area. *(approx. 20 minutes)*	AA	[redacted]
Document Review	-	Inspectors only

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PHARMACOVIGILANCE INSPECTION PLAN

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Implementing approved safety updates to product information To cover: - Process steps from variation approval to implementation - Pharmacovigilance oversight of the implementation of leaflet updates - Provision of current product information to relevant stakeholders including for medical information and publishing on eMC website	AA	[redacted]
LUNCH	-	

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PHARMACOVIGILANCE INSPECTION PLAN

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Safety variation management: To cover: - Identification of triggers to update product safety information - Submission of safety variations - Tracking and compliance management	BW	[redacted]
Document Review	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Accord Healthcare Ltd	**DATE**	29 January 2020

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PHARMACOVIGILANCE INSPECTION PLAN

LOCATION	Sage House, 319 Pinner Road, Harrow, HA1 4HF		**START TIME**	09:00
Purpose of Interview		**Session Lead**	**Staff to be interviewed**	
Document review and ad hoc interview sessions as required		-		
LUNCH		-		
Document review and ad hoc interview sessions as required		-		
Inspectors meeting		-	Inspectors only	
Closing meeting		-	All welcome	