Medicines & Healthcare products
Regulatory Agency

PHARMACOVIGILANCE
INSPECTION REPORT

Pharmacovigilance System Name: Janssen Pharma

MHRA Inspection Number: Insp GPvP 242/23473-0022

10 South Colonnade, Canary Wharf, London E14 4PU **T** 020 3080 6000 **E** gpvpinspectors@mhra.gov.uk
www.gov.uk/mhra

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ABBREVIATIONS

aRMM	Additional Risk Minimisation Measures
DHPC	Direct Healthcare Professional Communication
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
MAH	Marketing Authorisation Holder
PSMF	Pharmacovigilance System Master File
PV	Pharmacovigilance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SOP	Standard Operating Procedure
UAT	User Acceptance Testing
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection of the [redacted] additional risk minimisation measures
System(s) inspected:	Janssen Pharma [redacted]
Site(s) of inspection:	50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG
Main site contact:	[redacted] BioResearch Quality and Compliance (BRQC) Quality Assurance Inspection Management, 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG Phone: [redacted] Mobile: [redacted] Email: [redacted]
Date(s) of inspection:	12 June 2023 (remote inspection day) 13 – 15 June 2023 (onsite)
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted] [redacted]
Previous inspection date(s):	16 – 19 May 2022 21 – 25 August 2017 20 – 24 August 2012 9 – 12 June 2008 9 – 11 January 2007 27 February – 2 March 2006 15 – 19 November 2004
Purpose of inspection:	Inspection of the additional risk minimisation measures for [redacted] (educational materials and controlled access programme)
Products selected to provide system examples:	[redacted], authorised nationally in Great Britain and as an EU centrally authorised product in Northern Ireland
Name and location of UK QPPV:	[redacted] Janssen Cilag 1 rue Camille Desmoulins 92130 Issy les Moulineaux France Telephone: [redacted] Mobile: [redacted] Email: [redacted]
Global PV database (in use at the time of the inspection):	[redacted] (commercially available)
Key service provider(s):	Development, validation and ongoing maintenance of the Register and Alert System outsourced to eClinical Health.
Inspection finding summary:	0 Critical findings 1 Major finding

	1 Minor finding
Date of first issue of report to MAH:	21 July 2023
Deadline for submission of responses by MAH:	25 August 2023 Follow-up 1: 06 October 2023 Follow-up 2: 24 October 2023
Date(s) of receipt of responses from MAH:	25 August 2023 Follow-up 1: 06 October 2023 Follow-up 2: 24 October 2023
Date of final version of report:	26 October 2023
Report author:	[redacted], Pharmacovigilance Inspector Responses assessed by: [redacted] Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Janssen Pharma (Janssen) was selected for inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review the [redacted]) additional risk minimisation measures (aRMMs) obligated as part of the conditions of the marketing authorisation to ensure safe and effective use of the product. Compliance was assessed against currently applicable UK and EU pharmacovigilance regulations and guidelines. In particular, reference was made to The Human Medicines Regulations 2012 as amended, Regulation (EC) No 726/2004 as amended, Commission Implementing Regulation (EU) No 520/2012 and the EU good pharmacovigilance practices (GVP) Modules as modified by the guidance note 'Exceptions and modifications to the EU GVP that apply to UK MAHs and the licensing authority'. The commitments made in the [redacted] RMP UK-specific Annex (version [redacted] signed 03 May 2022) for the aRMMs and the approved protocol for the Patient Register and Alert System (version [redacted] dated 21 March 2022) were also taken into account.

A list of reference texts is provided in Appendix I.

Janssen is a wholly owned pharmaceutical company of the multinational healthcare company Johnson & Johnson. With headquarters in Beerse, Belgium, Janssen focuses on innovative medicines in therapeutic areas such as neurology infectious diseases, vaccines, immunology, oncology and cardiovascular and metabolic disorders. Pharmacovigilance (PV) activities are the responsibility of the Global Medical Organisation and the associated groups: Global Medical Safety, Established Products, Strategic Operations Support, and Patient Strategies and Solutions. Global Medical Safety activities are conducted at several sites in the USA and across Europe. In the UK, these activities are based at the High Wycombe office. Janssen is the UK MAH for [redacted] the focus of this inspection.

[redacted] is an [redacted] used as an antidepressant. The product was first authorised as a centrally authorised product on 18 December 2019 within Europe and since the UK's transition from the EU, the PLGB license was granted on 04 November 2022: [redacted]. As [redacted] is the [redacted] there is the similar potential for recreational drug abuse. Within the UK, [redacted] is a controlled drug under Schedule 2 of the Misuse of drugs Act 1971 and can only be dispensed in the healthcare setting where administration takes place. The product is currently on the MHRA additional monitoring list and the RMP contains specific conditions of the license which include the implementation of aRMMs to address important identified risks of:

- Drug abuse
- Transient dissociative states and perception disorders
- Disturbances in consciousness
- Blood pressure increased

Due to these risks, it is important that the product is prescribed by a psychiatrist and as part of the conditions of the licence, administered in a healthcare setting where the patient can be monitored and overseen by a trained healthcare professional (HCP).

[redacted] aRMMs in the UK

The aRMMs required within the RMP UK-specific Annex (version [redacted], signed 03 May 2022) to be implemented include educational materials and a controlled access programme.

Educational materials consist of a:

- Healthcare Professional Guide to educate HCPs on all important risks
- Patient Guide to educate patients on all important risks
- Healthcare Professional Checklist to support HCPs decide on when a patient may leave the post-administration monitoring setting.

The controlled access programme is required to minimise the risk of drug abuse and in the UK this takes the form of a patient registry, the [redacted] Register and Alert System. The system is intended to mitigate the risk of abuse through patient registration and generation of system alerts, which enables prescribers to identify patients who have received [redacted] at other centres (and thus avoid 'doctor shopping').

The Register and Alert system platform went live on 01 April 2022 after receiving approval from the MHRA on the design and proposed functioning. The system became mandatory for HCPs wishing to administer [redacted] following the distribution of a DHPC and updated educational materials on 20 April 2022. Janssen had obtained the services from eClinical Health to develop and provide ongoing support for the platform.

Functioning of the Register and Alert System

HCPs would be made aware of the platform either from previous awareness from the DHPC distribution or when an institution placed their first order for [redacted] as the DHPC and educational materials would be sent to the customer which explained the need to use the platform. HCPs would register with the platform and following validation of their credentials as a genuine HCP trained in psychiatry, they could create patient records on the platform, recording patient first names, surnames and date of birth. For each patient, the HCP could add the dates that the course of [redacted] treatment would start and then the end date of treatment. The system worked to prevent 'doctor shopping' as if a HCP entered the exact same patient details (first name, last name and date of birth) as a patient already registered on the system by a different HCP, the HCP would be alerted to contact the other HCP to confirm whether or not there was indeed a case of doctor shopping. The HCP causing the alert to appear was responsible for recording the outcome of this discussion as either:

- Confirmed alert (the patient was illegitimately seeking treatment at a second institution (doctor shopping)) – in this case, the HCP could take no further action within the system for the patient and should know not provide them with product.
- Patient transferred (the patient was registered at another institution but legitimately sought treatment at a new institution (due to a change of address etc.)) – in this case the patient record would be completely transferred to the new HCP in the system, who could then add treatment details for the patient on the system and could provide product.
- Legitimate duplicate (the patient has the exact same name and date of birth as another patient record on the system but the HCPs involved confirmed that these are valid duplicate records for two different patients) – the HCP could continue to use the platform as normal and provide product.

Janssen maintained oversight of the platform through extracting monthly reports on the number of institutions and patients registered on the system, and conducting reconciliation of this data against a monthly distribution report from Janssen Customer Service team, detailing where product had been supplied to for that month. Where discrepancies were identified (product had been supplied but no matching institution was registered on the system), Janssen

took actions, such as obtaining an acknowledgement of receipt of the educational materials. This provided some assurance that HCPs were aware of the risks and would dispense and administer product in the right setting. It is important to note that Janssen only had access to a specific view of the system to extract reports with pseudonymised data – they had no visibility of the actual data held in the system. The system generated reports Janssen were able to view and download as Excels were:

- System Report – displaying a list of institutions with at least one prescriber registered in the system and at least one patient registered on the system for the analysed period.
- System Output – displaying the number of prescribers, patients (with status of treatment) and system alerts. These reports were also termed 'prescriber-patient-alert reports'.

Janssen were also required to provide two 6-monthly reports of the system to the MHRA from the date of launch, and after this time, annual reports were required. Data presented in these MHRA reports comprised of the system generated reports for that time period, distribution reports and a summary on the number of alerts generated by the system along with a discussion from the MAH on this analysis. At the time of the inspection, two reports had been provided to the MHRA:

- 6-month report for April – September 2022 (submitted to MHRA on 30 November 2022)
- 6-month report for October 2022 – March 2023 (submitted to MHRA on 31 May 2023)

At the time of inspection preparation (19 May 2023), a total of 23 unique patients were registered on the system by 9 prescribers (associated with specific institutions). 18 prescriber accounts had been set up overall for which four had not yet been activated.

B.2 Scope of the inspection

The inspection included a review of the local (UK) implementation of the [redacted] aRMMs, as well as the systems and processes supporting the Register and Alert System. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II). The inspection was conducted at Janssen's offices in High Wycombe, UK. Personnel from eClinical Health also attended the site in order to participate in the inspection and the [redacted] MHRA Assessor, [redacted] attended the sessions on day 1 remotely.

The inspection was performed using interviews and document review, supported also by demonstrations of the Register and Alert System. The user acceptance testing (UAT) interface, Janssen's report extraction view and the live production environment were demonstrated to inspectors. Only eClinical Health were able to be present to show inspectors the live production environment due to the visibility of patient level data. For information, eClinical Health's regular view of the live system does not show any patient level data, only that at an institution level (all patient details are blanked out). However, for the purposes of inspection, patient level data was made visible to inspectors in order to verify the functionality of the system.

B.3 Documents submitted prior to the inspection

The company submitted a UK PSMF (version [redacted] dated 26 April 2023) 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, the detail of which can be found in document request sheet A and B.

B.4 Conduct of the inspection

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

A closing meeting was held to review the inspection findings at Janssen's offices, High Wycombe on 15 June 2023. At this point only two document requests were outstanding (F2 and L1) which were reviewed by inspectors in the following weeks with no change to the feedback already provided at the closing meeting.

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

No significant changes had been made since the last MHRA PV inspection in May 2022.

C.2 Definitions of inspection finding gradings

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

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

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

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

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

Findings from any inspection that covers products authorised in respect of Northern Ireland which are graded as critical or major will be shared with the EMA, EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

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

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

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

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

C.4 Inspection findings

C.4.1 Critical findings

No critical findings were identified from the processes, procedures and documents reviewed during this inspection.

C.4.2 Major findings

MA.1 Validation, functionality and reporting of the Register and Alert System

Requirements:

GVP Module I – Pharmacovigilance systems and their quality systems (as modified by the Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority)

I.B.8. Facilities and equipment for pharmacovigilance
"Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose."

eClinical Health was responsible for the development and ongoing maintenance of the electronic platform hosting the Register and Alert System. Testing of the system had been conducted by both eClinical Health and Janssen to ensure the user requirements specifications had been met.

During the inspection the functionality of the system was demonstrated, displaying the UAT and production environment to inform the inspectors how HCPs use the system, and also the Janssen view of the system reporting tools.

Isolated deficiencies with the system validation, functionality and reporting were identified.

Finding MA.1 a)

The prescriber-patient-alert reports extracted from the system presented inaccurate figures for the number of unique patients registered per prescriber.

The following was identified on inspection which impacted the reports extracted from the system used for Janssen oversight and to support the production of the MHRA reports. As Janssen do not have visibility of patient level data and there was no other routine quality check of this level of data completed by eClinical Health, this could not have been identified outside of the inspection, resulting in this being raised as a major finding.

i. A patient record #[redacted] was created by an initial prescriber at the [redacted] (site [redacted]) and then a duplicate record #[redacted] for the same patient was created by a different prescriber following which an alert was raised. This alert was resolved through transferring the duplicate patient record #[redacted] to the initial prescriber. Although patient record #[redacted] was essentially inactive following the transfer (the initial prescriber continued to use record #[redacted] , as it remained on the system (it could not be deleted or marked as void), the patient record was shown as a registered patient in the subsequent system prescriber-patient-alert reports. This meant that in the MHRA 6-

monthly report dated October 2022 – March 2023, two registered patients were listed against this institution, which was not correct and there was no statement in the report to explain as such.

ii. Multiple patient records had been created for the same patient at the institution [redacted] (site #[redacted]) due to the misunderstanding of the prescriber on how to use the system. The prescriber had created several patient records for the patient's different courses of treatment; the initial patient record was #[redacted] but records #[redacted], [redacted] and [redacted] were duplicates for different treatment courses. Alerts were appropriately raised in the system to the prescriber who logged the outcome of 'legitimate duplicate' so were able to input treatment data for the patient records. Yet this impacted the number of patients listed against this institution in the reports pulled from the system since those records had been entered. For example, the prescriber-patient-alert report for May 2023 showed that this institution had six patients registered in total, whereas it was confirmed by inspectors through review of patient level data that four of those patients were duplicates of patient record #[redacted]

iii. Further to point ii., it was identified that patient record #[redacted] entered by the same prescriber held no patient details (the fields were all blank in the system). However this appeared as a valid registered patient in the subsequent prescriber-patient-alert report including the data that would be presented in a future report to the MHRA. This is inappropriate as it does not give a true reflection of the number of actual patients registered on the system and the data could potentially be skewed due to invalid patient records being included in the calculations.

For information, the MHRA report for October 2022 – March 2023 was not impacted by the issues described in ii. and iii. as these patient records were created after this reporting period.

[redacted]

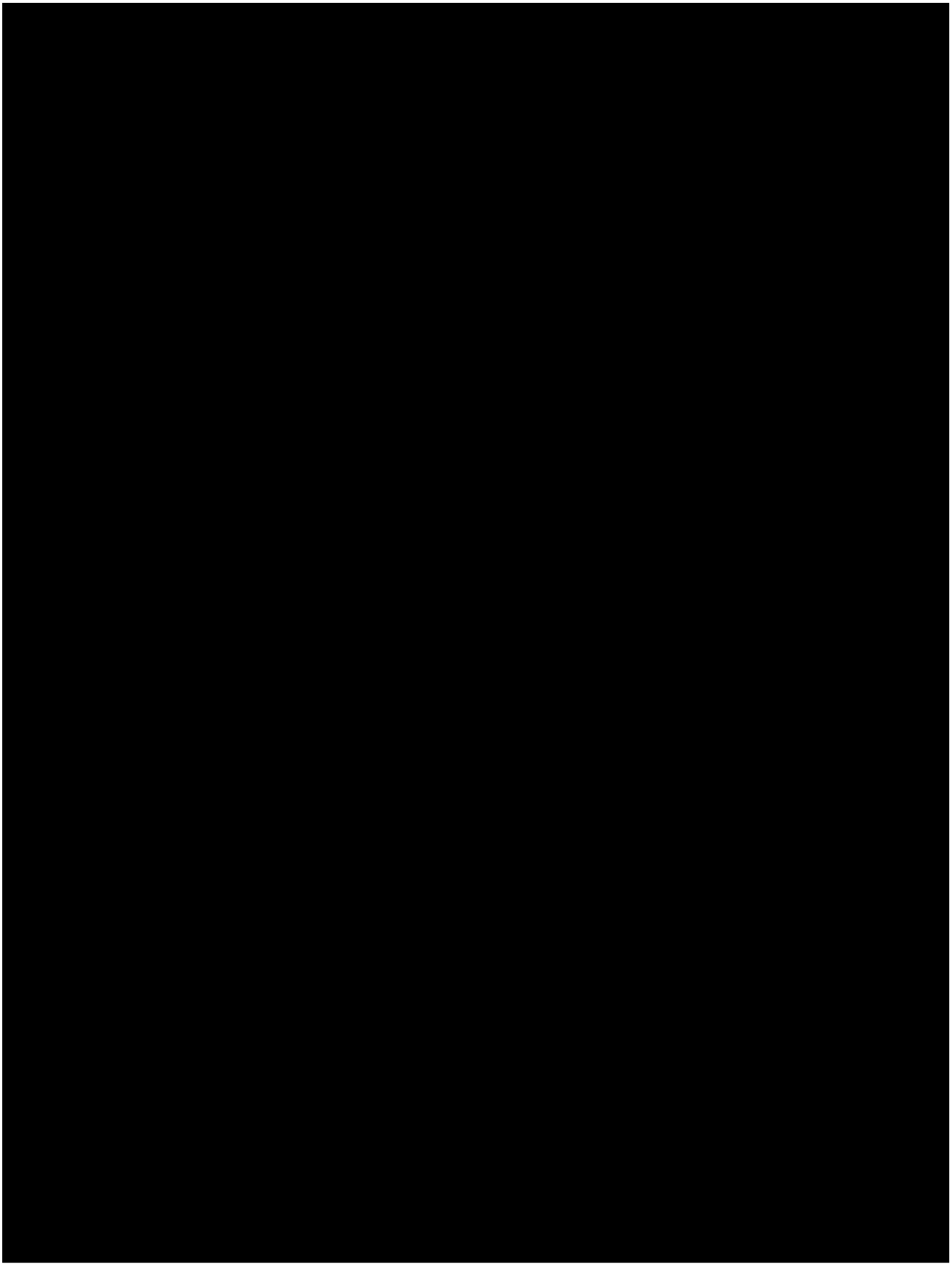
[redacted]

[redacted]

[redacted]

Finding MA.1 b)
A deficiency was identified regarding system functionality in line with the design specifications for the Register and Alert System. The 'Requirements and Design Specifications [redacted] Register and Alert System' (version [redacted] dated 24 March 2022) specifications document stated that in the scenario where no treatment end date was entered for an ongoing course of treatment, a reminder email was intended to be sent to the prescriber recurringly every three months after the initial triggering treatment start date was entered. Similarly, an in-system dashboard alert would appear to the prescriber under the same scenario and timeframes. It was identified that for the institution [redacted] (site # [redacted] with patient # [redacted] that the automatic email was not sent. A treatment start date for the patient of 25 February 2023 was recorded (entered onto the system that same day) but no treatment end date had yet been recorded. In line with the specifications document, the first reminder email should have been sent automatically to the prescriber on 26 May 2023 but according to the system, no such email had been sent. It was seen that the in-system dashboard alert to the prescriber had been triggered correctly on 26 May 2023. It is acknowledged that Janssen provided information that a reminder email regarding a missing treatment end date had been sent to the same prescriber for a different patient (# [redacted] on 31 May 2023. Therefore, Janssen should confirm whether the missing email explained above for patient # [redacted] was only an isolated occurrence rather than a systematic issue.

[redacted]



C.4.3 Minor findings

MI.1 Quality management system

Finding MI.1 a)
The following deficiencies were identified in relation to general PV requirements which eClinical Health staff must be aware of to fulfil their functions: i. No general PV training was given to eClinical Health staff that were responsible for operating the [redacted] Register IT Helpdesk, which could be reached via email and telephone. While it is acknowledged that the system's front page included a link to specific contact details for adverse event reporting, there is potential that adverse event reports may be received via the IT helpdesk. As such there should be training for relevant personnel and supporting procedures regarding how to handle safety reports to allow compliance by Janssen with UK PV requirements. ii. Neither the Master Services Agreement (effective 01 February 2021) or the Work order (effective 09 March 2021) between Janssen and eClinical Healthcare included provisions regarding general PV requirements, such as the exchange of adverse drug reaction reports or product quality complaints.

[redacted]

[redacted]

Finding MI.1 b)

Minor deficiencies were identified regarding the training of internal and external staff involved in the functioning of the system.

i. No training records were available to demonstrate that eClinical Health staff involved in the operation and maintenance of the Register and Alert System were trained on the joint operation guidelines pertaining to the set-up, management and technical support of system users.

For example the following procedural documents would be important for eClinical Health staff to be trained on:

- [redacted] (v1[redacted] dated 30 March 2022)
- [redacted] (Janssen and eCH) (v[redacted] date effective 20 April 2022)
- [redacted] (v[redacted], date effective 09 May 2022)

During the inspection, the eClinical Health representative stated verbally that training was provided to all relevant staff, but this had not been documented.

ii. Training of Janssen staff working on the [redacted] Register and Alert System was not complete:

a. The Evidence and Generation Lead was not trained on [redacted] Work Instruction' (version [redacted] effective date 25 March 2022). Janssen stated that no training was required as the Evidence and Generation Lead was not involved operationally in the system; however, the work instruction listed in the section 'Applicable Groups' that the Evidence Generation Lead must read and understand the procedure.

b. The Senior Medical Advisor was not trained on the following relevant procedures:

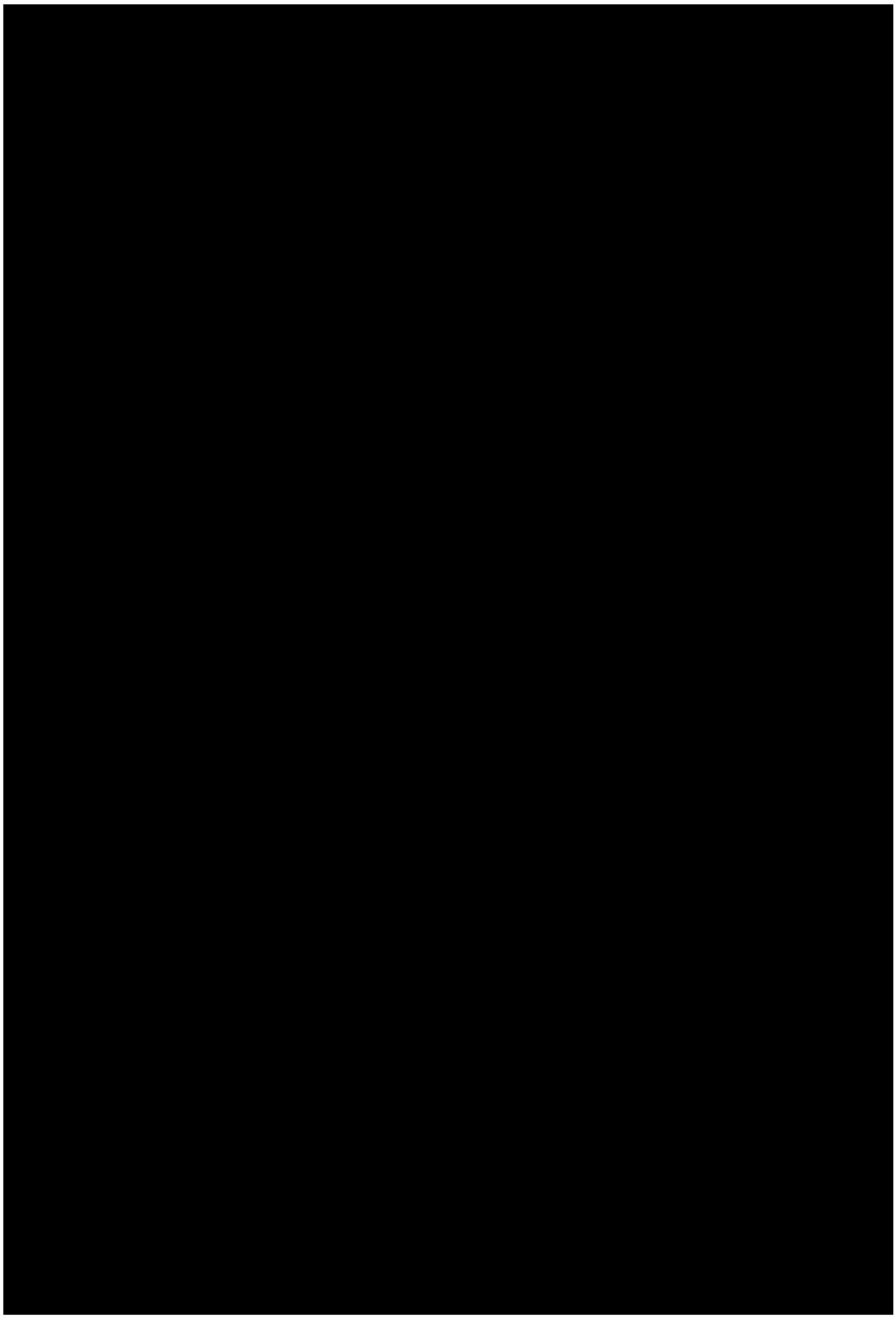
- [redacted]' (version [redacted] effective date 31 March 2022), which was applicable to all employees responsible for the implementation, retirement, tracking, and oversight of additional risk minimisation activities.
- [redacted] (version [redacted] effective date 20 April 2022), which described the effectiveness check of the [redacted] register via reports run from the system. The Senior Medical Advisor had carried out the associated responsibilities since March 2023. It is acknowledged that Janssen stated that all activities were delivered under supervision of the Medical Lead who was trained on the process.

c. The Medical Lead was not trained on the following relevant procedures:

- [redacted]' (version [redacted] effective date 31 March 2022), which was applicable to all employees responsible for the implementation, retirement, tracking, and oversight of additional risk minimisation activities.
- [redacted] (version [redacted], effective date 20 April 2022), which detailed that the Therapeutic Area Head or "delegate (a Medical Lead)" were responsible for notifying eClinical health of any Janssen staff leaving the company to revoke access to the [redacted] register.

[redacted]

[redacted]



C.4.4 Recommendations

1. There was minimal guidance in Janssen's SOP and work instructions associated with the system on how reconciliation would be conducted and what actions would be taken following reconciliation each month. Although verbally the process was described clearly and evidence was seen where this was repeatedly being followed, the below points would be beneficial to include in the (version dated 20 April 2022) or supporting instructions to ensure reconciliation is conducted consistently:
   - There was no mention that a monthly meeting would be held to discuss reconciliation outcomes, it only stated that multifunctional review of the data would occur.
   - There was no guidance to staff on how to use the Janssen interface of the system in order to extract reports and no explanation on what date range to select for each report period.
   - There was no explanation on how to pull together the data to create the reconciliation report. In practice, it was manually created by pulling data from the distribution report and system report together but only stated *"Prepare reconciliation report based on System report and Distribution Report"*
   - There was minimal explanation on what actions would be taken should reconciliation identify institutions supplied product who had no prescribers registered.

2. The MHRA reports for April – September 2022 and October 2022 – March 2023 presented reconciliation data on where institutions were supplied product in the period against the number of prescribers and patients registered for those institutions on the Register and Alert System. The data displayed to show institutions that were supplied product was under the column "Count of final delivery points" which essentially appeared as "1" to signify that at least one delivery to an institution had been made. It is recommended that the volume of deliveries (i.e. how much product had been supplied) is included so that the extent of institutions ordering product but not signing up to the system can be more easily visible to MHRA Assessors. This could provide a proxy of where institutions are dispensing product to patients but not signing up to the system. To note, the distribution report was also provided with the MHRA reports but this data is separate to the reconciliation report.

3. At the time of the inspection, the Register and Alert System was set up so that an alert for a potential duplicate patient would only be triggered if the combination of a patient's first name, last name and date of birth were an exact match between two registered patients. The protocol ([redacted] version [redacted] effective 20 April 2022) and the [redacted] Register User Guide ([redacted], version [redacted] effective 20 April 2022) stated that the patient's full legal name (including middle names) should be entered and no abbreviations were permitted. However, the system did not take into account slight variations in the patient's name (e.g. the omission of umlauts or hyphens, omission or inclusion of middle names). Therefore, there is potential that duplicate patient registrations would not be picked up in these scenarios which may occur due to human error or lack of technical knowledge to include rare special characters.

4. At the time of the inspection, Janssen and eClinical Health were in ongoing discussions to determine the scope, extent and nature of data transfer of the Register and Alert System data to Janssen in the event of platform decommissioning. Janssen are reminded to consider in future discussion their obligations as the MAH of [redacted] and that data on the register for patients and prescribers, as well as at the level of an audit trail, must be guaranteed for the lifetime of the marketing authorisation plus ten years to allow demonstration of the fulfilment of the controlled access programme and allow supervision by the MHRA.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

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

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

APPENDIX I REFERENCE TEXTS

- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916) as amended.
- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Commission Implementing Regulation (EU) No 198/2013.
- Guideline on good pharmacovigilance practices (GVP).
- Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority.
- CPMP/ICH/5716/03: ICH guideline E2E “Pharmacovigilance Planning”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DATE**	12 June 2023 (remote pre-inspection) 13 – 15 June 2023 (onsite)
PHARMACOVIGILANCE INSPECTION OF	Janssen – [redacted] RMS	**START TIME**	09:00
LOCATION	50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG	**INSPECTION TEAM**	[redacted] (lead inspector), [redacted], [redacted] (MHRA Assessor)

This inspection will be focused on a review of the [redacted] risk management system. Specifically:

- Educational materials: healthcare professional guide and checklist, the patient guide
- Controlled access programme
- [redacted] Register and Alert System:
  - Development, validation and maintenance of the system
  - Functionality of the system
  - Management and reporting of the system

Conduct:
A pre-inspection day will be conducted remotely by the inspection team which will be focused on document review.

The inspection plan below outlines the Opening Meeting and the one interview session required to orientate inspectors around the systems and processes in place for [redacted] The remainder of the inspection will consist of document review and further document requests will be submitted throughout the course of the inspection. Additional ad hoc discussions with company personnel will also be required. Please ensure that subject matters experts are available and indicate any times personnel may be unavailable in the relevant sections below. The lead inspector will liaise with the designated inspection host to arrange ad hoc discussions as required.

Access to view live systems used in the activities under review may also be requested.

The inspection will finish with a closing meeting on Thursday 15 June (time to be confirmed) when verbal feedback will be provided from the inspection. All relevant personnel are welcome to attend the closing meeting.

Tuesday 13 June 2023	
Opening Meeting 09:00 GMT/BST, led by the lead inspector The agenda will be: • Review of scope of inspection and inspection plan (lead inspector) • Janssen are asked to provide a brief company presentation (max. 20 minutes) which aims to provide the inspectors with an overview of the risk management system for [redacted] the supporting quality system and the key parties implementing and running the system.	
***Session 1** – 11:00* GMT/BST **Overview of the controlled access programme and the [redacted] Register and Alert System** to include: • Implementation of the controlled access program and distribution of product • A demonstration of the Register and Alert System • Initial set up and registration of prescribers and patients on the system	Interviewee(s): Fyi Video links providing an overview of the system have already been shared with MHRA. As discussed,: [redacted] can provide a demo of the UAT environment. [redacted] can demo the Janssen view in the Production environment. [redacted] – Head of Customer Services [redacted] – UK Quality Head

• Access to educational materials on the system	[redacted] – Evidence Generation Lead and eClinical Health [redacted] (Eclinicalhealth) -
• Ongoing management of the system (e.g. extraction of data, management of alerts, reminders, maintenance of the system and business continuity measures)	[redacted] – Senior Medical Advisor, Neuroscience [redacted] – Evidence Generation Lead [redacted] – Senior Medical Advisor, Neuroscience [redacted] – Evidence Generation Lead [redacted] – Medical Lead, Neuroscience [redacted] – Head of Customer Services [redacted] – Regulatory Consultant
Additional demonstrations of the Register and Alert System by the eClinical Health specialist for the inspection team took place on the following dates and times: • *13 June 2023, 15:00 to review non-anonymised data at prescriber level* • *14 June 2023, 09:30 to review non-anonymised data at patient and prescriber level* • *14 June 2023, 11:00 to review automated email and in-system alerts for prescriber[redacted] and patients #[redacted] #[redacted] and #[redacted]* • *15 June 2023, 15:30 to review the system audit trail for automated email and in-system alerts for prescriber[redacted] and patient #[redacted]*	

A further interview was held with Janssen IT staff ([redacted]) on 14 June 2023 at 11:30 to discuss Janssen's involvement in the sign-off of the platform and system decommissioning plans.

Contact Point

Please state the designated inspection contact point, the opening meeting attendees and list personnel who will be available for interview/ad hoc questions regarding the specified topics; including job title and subject matter expertise. Please indicate any time zone differences. Notes may also be added for individuals to indicate any periods of unavailability during the inspection.

Designated contact point:

[redacted], BioResearch Quality and Compliance (BRQC) Quality Assurance Inspection Management, [redacted]

Opening meeting attendees:

The following people will attend in person and some additional people may join via TC.

As above (see session 1 attendees) plus

[redacted] [JRDGB][redacted], Country Medical Safety Team Lead

[redacted] [JACGB][redacted] Therapeutic Area Medical Director Neuroscience

[redacted] [JRDGB][redacted]

[redacted] Project Manager and System Architect

[redacted] [JRDGB][redacted]

[redacted] [JACGB][redacted]

[redacted] [JACGB][redacted]

[redacted] [JACGB][redacted]

[redacted] [JACGB][redacted];

[redacted] [JACGB Non-J&J][redacted]

Subject matter experts (by topic):

As above (see session 1 attendees).

N.B. The inspection plan may need to be amended before or during the inspection.