Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Ethypharm

MHRA Inspection Number: Insp GPvP 6934/17488-0003

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Heads of Medicines Agencies
EMA	European Medicines Agency
EU	European Union
GVP	Good Vigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
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
QA	Quality Assurance
QMS	Quality Management System
QPPV	Qualified Person responsible for Pharmacovigilance
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SmPC	EU Summary of Product Characteristics
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Section 40 and 43

Inspection type:	Re-inspection
System(s) inspected:	Ethypharm, [redacted]
Site(s) of inspection:	Building A2, Glory Park, Glory Park Avenue, Wooburn Green, High Wycombe, HP10 0DF
Main site contact:	[redacted]
Date(s) of inspection:	09-12 July 2019
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	05-09 February 2018, Martindale Pharma (now part of Ethypharm) (Reference number: [redacted] 16 January & 22 February 2017 Viridian Pharma (now part of Martindale Pharma) (CHMP requested inspection that was subsequently cancelled but a report was produced – see section B.1. Reference number: [redacted] 19 March – 21 March 2012 Aurum Pharmaceuticals (as part of Martindale Pharma) (Reference number: [redacted] 19 March – 20 March 2007 Martindale Pharma (Reference number: [redacted]
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):	SafetyE@sy (leased from AB Cube by AnticipSanté)
Key service provider(s):	Pharmacovigilance activities are performed by the MAH. Deputy QPPV and database administration services are provided by AnticipSanté.
Inspection finding summary:	1 Critical finding 2 Major findings 1 Minor finding
Date of first issue of report to MAH:	27 August 2019
Deadline for submission of responses by MAH:	30 September 2019
Date(s) of receipt of responses from MAH:	30 September 2019, 23 October 2019
Date of final version of report:	25 October 2019
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Martindale Pharma was selected for reinspection as a result of two critical findings that were identified during the previous routine inspection of the MAH, performed on 05-09 February 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 the pharmacovigilance system 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 good pharmacovigilance practices (GVP) Modules. A list of reference texts is provided at Appendix I.

Ethypharm is a global organisation with a commercialised portfolio focused on medicines for pain, addiction and use in critical care settings. Ethypharm acquired Martindale Pharma in February 2017 and the products held by the Martindale group of companies (Macarthys Labs, Martindale, Aurum and Viridian) have been transitioned from the previous PV system maintained by Martindale Pharma [redacted] into the Ethypharm PV system [redacted] in March 2018.

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Pharmacovigilance activities for UK marketing authorisations are conducted in house by teams in the UK (Ethypharm UK) and in France (Ethypharm SAS). Maintenance and administration of the safety database, as well as the services of a backup QPPV and medical advisor, are provided by the service provider AnticipSanté.

B.2 Scope of the inspection

The inspection included a review of the local (UK) and global pharmacovigilance systems and was performed at Ethypharm UK's offices in High Wycombe, Buckinghamshire. Personnel from Ethypharm SAS attended the High Wycombe site and connected by web conference in order to participate in the inspection.

The inspection focussed on a review of the systems and processes which were associated with the deficiencies/critical and major findings identified during the previous inspection in relation to risk management activities, ongoing safety evaluation and management of safety data. The maintenance of the safety sections of SmPCs and PILs was also reviewed.

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

B.3 Documents submitted prior to the inspection

The company submitted a PSMF [redacted] dated 29 May 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 full list of personnel interviewed during the inspection has been provided by Ethypharm and appended to the report in Appendix II. Two additional days were used to remotely complete the review of inspection documentation after the days spent on site.

A closing meeting was held to review the inspection findings at Glory Park, High Wycombe on 12 July 2019.

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

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

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

- Pharmacovigilance activities were brought in house from the previous service provider PharSafer in March 2018.
- A data clean up project was conducted for cases received prior to March 2018 as part of the migration of historical cases from the former global safety database maintained by PharSafer (Argus) into the Ethypharm global safety database (SafetyE@sy), which was completed on 18 December 2018.
- The products held by the Martindale group of companies (Macarthys Labs, Martindale, Aurum and Viridian) were transitioned from the previous PV system maintained by Martindale Pharma [redacted] into the Ethypharm PV system [redacted] in March 2018, together with the integration of other business activities including regulatory affairs and commercial activities.

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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

At the time of re-inspection, evidence was provided to support that the critical deficiency identified during the previous inspection relating to a failure to conduct signal detection for a large proportion of the products in the Martindale portfolio had been resolved. Ethypharm had completed a project to perform a documented cumulative safety review, considering appropriate sources of data, for every Martindale portfolio product. However, a major finding in relation to the current process for signal detection and management has been reported (please refer to MA.2).

The critical finding identified during the previous inspection relating to risk management had not been sufficiently addressed and therefore it remained as a critical deficiency.

CR.1 Implementation of additional risk minimisation measures

Requirements:

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

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

GVP Module III Pharmacovigilance inspections
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."*

GVP Module V Risk management systems (Rev 2)
V.B.3 Overview of the format and content of the risk management plan
"It is recommended, where appropriate, that the RMP document includes all relevant medicinal products from the same applicant/marketing authorisation holder containing the same active substance(s) (i.e. the RMP is an active substance-based document) […]."

GVP Module XVI Addendum I – Educational materials
XVI. Add I.3. Provisions surrounding the submission of educational materials.
"If no other national requirements apply, the draft educational material should be submitted to the competent authorities of Member States as follows:

- *with a cover letter and/or request form including the following information:*
  - *a detailed implementation plan for the educational material with the following information:*
    - *target population(s);*
    - *dissemination method (e.g. paper, e-mail, via social media, learned societies and/or patient associations, publication on websites);*
    - *time point when dissemination is anticipated to start and frequency of further disseminations;*
    - *estimated date of launch or date of start of the marketing of the product (in the case of a new marketing authorisation);"*

At the previous MHRA inspection of the Martindale pharmacovigilance system in 2018, a critical finding was reported (CR.1) concerning deficiencies across the risk management system. During the re-inspection, a review of the remedial activities taken to address this critical finding identified that Ethypharm had failed to adequately address elements of this finding, specifically:

CR.1 a) *"Failure to implement additional risk minimisation measures for important identified and potential risks in accordance with the approved RMP"* in relation to the additional risk minimisation programme for Espranor (buprenorphine).

CR.1 e) (ii) *"Failure to maintain risk management plans in line with the known safety concerns and the current risk management system for the product"* in relation to unacceptable discrepancies between the two clobazam RMPs concerning the list of safety concerns.

The failures are detailed below in findings CR.1 a) and CR.1 b) respectively.

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Finding CR.1 a)

At the 2018 MHRA inspection it was identified that the [redacted] educational programme had not been implemented in the UK following product launch in January 2017.

The additional risk minimisation programme for [redacted] consisted of an educational programme for HCPs and patients to inform them about important risks of respiratory depression and overdose with [redacted] particularly when used in conjunction with other CNS depressants such as other [redacted]

The materials were also designed to emphasise that the route of administration of [redacted] is different to other [redacted] products and that there is an associated risk of medication errors that may result in overdose due to the potential for confusion between the different posologies.

At the time of the re-inspection in July 2019, over two and a half years since the product was launched, market share data confirmed that [redacted] s now over 50% of the [redacted] market and the [redacted] educational programme had still not been implemented in the UK.
Actions taken by the MAH since the 2018 MHRA inspection are summarised below:

- An update to the [redacted] RMP was prepared by Ethypharm to address findings from the 2018 inspection and submitted to the MHRA for assessment on 13 July 2018. The RMP [redacted] was approved on 10 December 2018.
- Mock-ups of the UK national educational materials were submitted to MHRA on 16 January 2019, along with a distribution plan. The distribution plan included the target population, but it did not fully specify the dissemination method or the time point when dissemination was anticipated to start and frequency of further disseminations. Instead it stated [redacted] *s sold to a small group of customers by the Marketing Authorisation Holder, which will allow for the rapid dissemination of the educational material via post or emails following company's procedure for dissemination."*
- Due to the lack of detail in the distribution plan, the MHRA Assessor requested the company's procedure for dissemination on 11 February 2019. [redacted] Risk Minimisation Measures Implementation, v3, effective 26 June 2019) was provided on 02 July 2019, five months after the request.

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This sequence of events resulted in a delay in finalising the approval of the national educational materials and consequently, an unacceptable delay in communicating these important safety messages to UK HCPs and patients.

The risk management system for [redacted] serves to proactively minimise the product's important risks. The failure to provide patients and healthcare professionals in the UK with MHRA approved materials on the known risks of [redacted] is not only considered to represent a serious violation of the legislative requirements to operate a risk management system in accordance with the risk management plan, as described in HMR regulation 182(2)(c), but also to adversely affect the rights of patients in accordance with paragraph 40 of Directive 2001/83/EC, which states that "*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*".

MHRA post inspection comment:
Due to the serious nature of this finding, after the inspection a letter was issued to Ethypharm by the MHRA Inspection Action Group (IAG) on 07 August 2019 (please refer to Appendix III). This letter stipulated immediate remedial action that was to be taken by Ethypharm, specifically to:

- Ensure the electronic availability of the [redacted] UK educational materials, namely the Health Professionals' Guide and Patients' Guide (approved by the MHRA on 19 July 2019) on the electronic Medicines Compendium within 5 business days of receipt of the letter.
- Expedite the initial hard-copy distribution of the aforementioned educational materials to the approved target recipients listed below:
  - Healthcare professionals (medical prescribers) including
    - NHS - psychiatrists (all grades), nurse prescribers and GPs with special interest in substance misuse
    - Pharmacists
    - Drug treatment services
    - Prison services

  Martindale Pharmaceuticals Limited should provide the MHRA with a detailed list of all recipients and their respective organisations, along with the planned/ actual dates for hard-copy distribution, within 10 business days of receipt of the letter.
- Confirm the date by which wholesalers will establish the alerts which are sent to customers every time an order is received for [redacted] within 10 business days of receipt of the letter.
- Ensure the documented training of all applicable Martindale Pharmaceuticals/ Ethypharm UK staff on the approved risk management system for Espranor (including on all associated procedural documents) within 15 business days of receipt of the letter.

Responses to this inspection finding should include how these actions have been addressed. Related documentation received prior to finalising the inspection report and closure of the inspection will be appended in Appendix III.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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[redacted]

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

Preventative Action(s)

[redacted]

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

Finding CR.1 b)
In the 2018 MHRA inspection, unacceptable discrepancies were identified between the two [redacted] RMPs relating to the list of safety concerns (CR.1 e). The CAPA due date for preparing a single updated RMP for all [redacted] products in the Ethypharm group portfolio and submitting to the competent authorities for all of the relevant MAs was **31 August 2018**. The company did not apply for worksharing for a grouped type II application to harmonise the RMP and SmPC for the two decentralised licences for [redacted] until **22 November 2018**. The worksharing application [redacted] was accepted by the CMDh on 13 December 2018. However, the RMP was not submitted for assessment until **13 February 2019**. This represented a delay of five and a half months from the CAPA commitment date.
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]	

Comment
It was noted that the current version of [redacted] (Additional Risk Minimisation Measures Implementation, [redacted] effective 26 June 2019), used as the plan for distribution of the [redacted] educational programme, did not include consideration of periodic re-distribution of educational materials to new prescribers and users, as per GVP Module XVI.B.3, which states *"a one-off distribution of educational tools may be insufficient to ensure that all potential prescribers and/or users, including new prescribers and users, are reached"*.

C.4.2 Major findings

MA.1 Maintenance of 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"*

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

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

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

Ethypharm were performing packaging and QP release for UK authorised products in house in France and the UK, and also using third party providers in the UK and France for certain products.

Finding MA.1 a)

The mechanisms in place for Ethypharm to ensure PILs containing updated safety information were being introduced in released batches of product in a timely fashion were insufficient. Guidance published by the MHRA states that once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months.

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

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During the inspection, a review of all safety-related updates to patient information leaflets in a 20 month period (01 March 2017 to 30 November 2018) identified evidence of the release of out of date PILs in batches for three products beyond the six month timeframe and, for two of these examples [redacted] significant delays in implementing the updated PILs into released batches were observed.

i) A type [redacted] variation fo[redacted] was

approved on 09 January 2018. Corresponding updates to the PIL included the addition of the following:

- Clarification regarding use during pregnancy and breastfeeding
- New contraindicated medicines
- New side effects to section 4
- The required wording on reporting of adverse reactions to MHRA via Yellow Card

Two batches (batch numbers: [redacted] were released containing the superseded version of the PIL on 12 February 2019, over 13 months after the approval of the updates.

ii) A type [redacted] variation for [redacted] was approved on 22 August 2018. Corresponding updates to the PIL included the addition of the following:

- CMDh recommended warnings concerning the concomitant use of [redacted] ike products and opioids
- Guidance for use in the elderly
- New side effects to section 4
- To section 5, the following wording: 'Do not use this medicine if you notice the tablets are discoloured or show signs of discolouration in any way.'
- The required wording on reporting of adverse reactions to MHRA via Yellow Card

Three batches o[redacted] were released beyond the six month timeframe, on 16 May 2019 (batch number: [redacted] and 03 June 2019 (batch numbers: [redacted]. The latest two batches were released over nine months after the approval of the Type [redacted] variation.

iii) Type [redacted] variations for [redacted] and [redacted] were approved 19 January 2018. These variations resulted in extensive and significant updates to the PIL, including the addition of a warning detailing potentially life-threatening skin rashes and the need to seek immediate advice from a doctor in the event of certain symptoms. Three batches o[redacted] were released beyond the six month timeframe with batch numbers [redacted] and [redacted] released on 31 July 2018 (nine days over the deadline) and batch [redacted] released 10 days over the deadline on 01 August 2018.

This finding has been graded as major rather than critical as these examples of non-compliance represent eight affected batches of four product presentations, compared with batches released compliantly for over [redacted] other product presentations that had undergone safety-related updates to the PIL during the period under review. Details of the affected batches were reviewed by the MHRA's Defective Medicines Reporting Centre (DMRC), and no further action was considered necessary (please refer to GPvP Post Inspection Letter dated 18 July 2019 in Appendix III of this report).

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Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

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[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

[redacted]	

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[redacted]

Finding MA.1 b)

The following non-compliance and delays in keeping product information up to date with the current scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal were identified:

i) In February 2018 the CMDh published advice that harmonised texts should be included within EEA product information concerning warnings on the concomitant use of [redacted] and [redacted] Proposed text for SmPC sections 4.4 and 4.5 and PIL section 2 was published for both [redacted] and [redacted] licences. The MHRA's expectation is that variations to update the safety sections of SmPCs and PILs are submitted within a maximum of six months of the identification date, unless a shorter timeframe has been stipulated by a regulatory authority. The corresponding safety variations should have therefore been submitted by August 2018. At the time of the inspection the following failures to comply were identified:

- A variation to update the codeine national licence had not been submitted [redacted] this product was marketed in the UK and the last batch was released on 17 June 2019.
- Variations to update the pethidine national licences were not submitted until 26 April 2019 [redacted] and 03 May 2019 [redacted] this delay was without adequate justification.

ii) In PRAC meeting 29 August to 01 September 2017, the Committee recommended that the product information for [redacted] should be updated to include a warning on axial dystonia in section 4.4 within 60 days of the publication date, which was 25 September 2017. The variation was not submitted to MHRA until 03 July 2019, a delay of over 21 months. The product is marketed in the UK.

This PRAC signal was not identified by Ethypharm during a retrospective review of PRAC recommendations performed between 28 - 31 August 2018.

iii) A PSUR Single Assessment (PSUSA) outcome published in March 2019 included an action for MAHs of [redacted] and [redacted] to include ADRs on [redacted] deficiency and delirium, and warnings concerning drug dependence in SmPCs and PILs. The timetable for implementation stated that a variation should have been submitted by 15 May 2019. A variation to update the [redacted] products was submitted on 04 June 2019, which represented a delay of approximately three weeks from the stated deadline. Both the [redacted] and [redacted] were marketed in the UK.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

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

Finding MA.1 c)
A review of the maintenance of Ethypharm product information published on the UK electronic Medicines Compendium (eMC) website showed that out of the five examples reviewed, there were delays of over three months in updating the information for two products: i) [redacted] for which a type [redacted] variation was submitted on 10 March 2017, the update was not submitted to eMC until 13 June 2017 for the PIL and 15 June 2017 for the SmPC. ii) [redacted] or which a type [redacted] variation was submitted on 23 March 2017, the update was not submitted to eMC until 30 June 2017 for the PIL and 05 Jul 2017 for the SmPC. It is the expectation of the MHRA that product information published on the eMC website is updated within 10 working days of updating the information. This was reflected in the Ethypharm Regulatory Affairs variation approval notification email template. For a type [redacted] 'do and tell' variation, this timeframe would start on the date that this variation was submitted.
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)**
[redacted]	

MA.2 Ongoing safety evaluation

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 4 (3) *"Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved."*

Article 18 *"(2) Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database. (3) Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information."*

GVP Module IX Signal management (Rev 1)
IX.B.2. Signal detection
"Signal detection should follow a methodology which takes into account the nature of data and the characteristics"

IX.B.5. Quality requirements, including:
"Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities."
"Through a tracking system, all organisations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale."
"The performance of the system should be controlled and, when used, performance indicators should be presented in the annex to the pharmacovigilance system master file."

IX.C.3.2. Periodicity of monitoring

GVP Module I Pharmacovigilance systems and their quality systems
I.B.6 *"For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for:* [...] *identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary"*

GVP Module II Pharmacovigilance system master file (Rev 2)
II.B.4.7. PSMF section on quality system

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Finding MA.2 a)

The [redacted] signal detection activities were reviewed during the inspection. This product was on the 'List of active substances involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders'.

The pilot period started on 22 February 2018, however Ethypharm had failed to conduct continuous monitoring of the data in EudraVigilance. The activities conducted to date

comprised a review of the data in EudraVigilance for the period 01 April 2018 to 30 September 2018, the results of which were discussed in the signal detection report dated 17 November 2019 (date error on report, year should be 2018). The company had failed to monitor the data in EudraVigilance between 22 February and 31 March 2018 and for the six month period following the activity reported in November 2019 (01 October 2018 to 31 March 2019).

Working Instruction INST PV-19 (Use of EVDAS, v1, implementation date September 2018) included a periodicity of *"at least every 6 months"* to download the eRMR from the EVDAS platform.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 b)

There were deficiencies in the written procedures EU HQ SOP [redacted] (Safety Monitoring and Signal Detection, [redacted] effective date 10 January 2019) and the UK-equivalent SOP [redacted] Safety Monitoring and Signal Detection, v1, effective date 31 July 2018) (section references given are from SOP [redacted] which did not meet the requirements laid out in GVP Module IX:

i. Section 5.1 (Review of cases or clusters, on a case-by-case basis) described a review of cases every two weeks to detect safety signals. There was no guidance for the reviewers of the case listings (i.e. Pharmacovigilance Scientist or Senior Pharmacovigilance Officer) for how to detect a signal from the bi-weekly review of cases. It was stated verbally that reviewers would be focussing on serious unlisted reactions and fatal outcomes when reviewing the case data.

ii. Section 5.3.1.2 (Methodology applied for cases review) included numerical thresholds for signal detection which were not considered to be appropriately sensitive to detect emerging signals. One of the signal criteria was stated to be "*More than 3 unlisted AR / AEs, relating to 3 different cases and falling within the same category (i.e. the same "preferred term") in the MedDRA medical nomenclature (or relating to a change in the severity, a new drug interaction, misuse, etc.)*" As examples, there were [redacted] cases in total in the global safety database and six dexamfetamine cases. Therefore, it may be more appropriate to expand the application of these numerical thresholds to

include similar medical concepts under MedDRA HLTs/HLGTs to better allow for the detection of emerging signals.

iii. The timelines for signal validation in section 5.4 (Signal validation/ assessment) were not considered to be appropriate. The Ethypharm signal validation process encompassed a combined validation and further assessment activity (as per GVP Module IX terminology) and the timelines for conducting signal validation were as follows:

- 1 month for signal quoted as "Urgent"
- 6 months for signal quoted as "As soon as possible"
- 1 year for signal quoted as "Non-urgent"

It is not considered appropriate to allow for up to one year to determine whether there are new risks causally associated with the active substance or medicinal product or whether known risks have changed. The MHRA expectation is that initial signal validation is performed within one month of detection of a potential signal and further assessment of validated signals is performed within three months. It would be expected that this timeframe is reduced accordingly when assessing important potential risks.

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Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

Preventative Action(s)
[redacted]

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

Finding MA.2 c)
There were examples of where the signal trackers were not accurate with respect to the status of signals: i. [redacted] – signal of cutaneous lupus erythematosus (CLE) (date detected 'Nov11/ Oct16'). The status on signal tracker was 'ongoing', however 'subacute CLE' is a listed ADR in the product information following a PRAC signal recommendation in 2015. The company could not explain why 'CLE' was still recorded on the tracker as ongoing. ii. [redacted] – signal of withdrawal syndrome in neonates (date detected 'Apr-2016'). This signal was raised in 2016 and status on the signal tracker was 'to be assessed'.

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This ADR is listed in the UK SmPC [redacted] Ethypharm and the MAH confirmed that the signal tracker should be updated to change the status of the signal "Withdrawal syndrome in neonates" as closed (identified risk).

iii. [redacted] – signal of dyspnoea (date detected '05-Jul-2017'). This signal had a status of 'ongoing' on the signal tracker, but the response provided by Ethypharm during inspection stated that the signal status should be 'to be assessed'. The MAH should confirm in the inspection response why this signal is still to be assessed two years following initial detection and provide corrective and preventative actions as appropriate.

iv. [redacted] – signal of cardiovascular risk of [redacted] (date detected '01/09/2017'). This risk was listed in the UK product information and under 'Action(s) taken or planned' on the signal tracker it was stated, 'To be discussed in the next PSUR'. However, the PRAC recommendation from procedure [redacted] was to update the product information with a warning on risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin, and the MAH submitted the associated variation on 27 April 2018.

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]	

Finding MA.2 d)

Ethypharm maintained a separate signal tracker for each active substance. There were examples of signal trackers that were not provided in response to request A5 ('The current signal tracker(s) (filtered for UK authorised products)'), despite evidence that there were signals for the products in question:

i. [redacted] The signal detection report dated 17 November 2019 (date error on report, year should be 2018) included a signal of serotonin syndrome in Appendix III (Signals tracker). This signal was as a result of a recommendation in the PRAC PSUSA report (for the PSUR DLP 11-Sep-2017 [redacted] However, a signal tracker was not provided in response to request A5.

ii. Signal trackers for [redacted] were not provided in response to request A5, despite the fact these products were in scope of the CMDh recommendation to update product information with a warning on the concomitant use of opioids and [redacted] For other applicable products this recommendation had been recorded on the signal trackers provided to the inspectors.

Root Cause Analysis

[redacted]

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[redacted]

Further Assessment
[redacted]

Corrective Action(s)	
[redacted]	

Preventative Action(s)	
[redacted]	

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

Finding MA.2 e)
Monitoring of the performance of the signal management process was deficient in the following ways: i. Performance indicators for the signal management process for global products were reviewed during the inspection. A number of non-compliances against procedural timeframes had been flagged in the KPIs; however, there was no evidence that a deviation had been recorded in the PSMF. For example, there were multiple examples of signal detection reports being reviewed and signed after the procedural timeframe of two months after the DLP in 2019. It was also noted that the PSMF did not have a placeholder for quality system deviations to be presented. ii. No performance indicators were in place for signal management activities for local products, despite the following statement in SOP [redacted] *"Performance indicators on the signal management process are put in place and made available to the UK Deputy EUQPPV and the UK Product Safety Committee."*

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iii. Annex F of the PSMF did not include the performance indicators for the global process.

Root Cause Analysis

[redacted]

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 f)

SOP [redacted] included a process for a quarterly prioritisation of active substances for signal detection activities; the outcome was documented in a report listing all active substances with their assigned priority for signal detection. Section 5.2.3 'Timelines' stated *"The "Report for signal detection activities prioritisation" shall be validated within the two months after the end of the previous quarter"*. There were delays in finalising the signal detection activities prioritisation reports that were reviewed during the inspection:

- [redacted] – report dated 30 June 2019
- [redacted] report dated 30 June 2019
- [redacted] – report dated 30 June 2019

It was also noted that the SOP did not include a maximum timeframe between signal detection activities, i.e. if an active substance was never prioritised in the quarterly reports.

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)
[redacted]	

C.4.3 Minor findings

MI.1 Maintenance of reference safety information

Finding MI.1 a)
There was no timeframe defined in written procedures for the submission of safety variations to align with the reference medicinal product information, to ensure the timely update of Ethypharm product information in line with current scientific knowledge. SOP[redacted] (Update of Product Information Documents, v2.0, effective date 01 August 2016) stated that the deadline for standard variations was no greater than six months after the date when a signal was confirmed internally or after the date of receipt by Ethypharm of information from a regulatory authority. Additionally, it was noted that submission deadlines in PSMF Annex F4 c) 'Submissions handled by UK Affiliates' were listed as 'Not applicable' for variations to align the Ethypharm product information with the reference medicinal product information.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
[redacted]

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Finding MI.1 b)
The [redacted] CCSI [redacted] dated 09 May 2017) included four drug interactions that were not included in the UK SmPCs [redacted] These were: ■ [redacted] ■ [redacted] ■ [redacted] ■ [redacted] The source of this information was a French document maintained by the French Medicine Agency (ANSM) called "*Thesaurus des interactions médicamenteuses*" that includes a list of interactions between drugs. The MAH stated that these interactions were not considered for inclusion in the UK SmPC

as they were not included in the product information of the UK reference product. In this situation when the MAH becomes aware of new safety information which is not included in the reference product information, it should notify the MHRA using the email address variationqueries@mhra.gov.uk to request advice on how to proceed, i.e. whether a Type II variation to add the new safety information should be submitted.

Root Cause Analysis

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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]	

Finding MI.1 c)

The processes for aligning the Ethypharm product information for its generic licences with that of the reference medicinal product were not adequate for achieving alignment with a suitable reference product. The MAH described a process whereby it had subscribed to alerts from the eMC to receive a notification when the product information for any comparator products for active substances that Ethypharm held a UK licence for had been updated, so that the update could be considered for inclusion in the Ethypharm product information.

The MAH should take account of the following points:

- For the duration of the time that the licence for the original reference medicinal product stated in the generic licence application dossier is active, Ethypharm should ensure alignment with this reference medicinal product licence only. The MAH should describe in the inspection responses how this will be achieved, i.e. process and periodicity of review of the reference product information.
- If the reference medicinal product licence is cancelled, Ethypharm should contact the MHRA using the email address variationqueries@mhra.gov.uk to request advice on a suitable replacement reference medicinal product for the active substance(s) in question. Following assignment of a suitable reference product, the MAH should implement a process to ensure alignment with this product information going forward (note, the initial alignment with the new reference product information will require submission of a Type II variation application).

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]	

C.4.4 Comments

The company should investigate with the safety database provider whether the PBRER summary tabulation query is extracting terms that are related (i.e. reactions) or both reactions and events. GVP Module VII.B.5.6.3. states *"This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR."*

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 12 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).
- CPMP/ICH/377/95: E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- CPMP/ICH/3945/03: E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: E2E "Pharmacovigilance Planning".

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Martindale Pharma/Ethypharm	**DATE**	09 July 2019
LOCATION	Building A2, Glory Park Glory Park Avenue Wooburn Green High Wycombe HP10 0DF	**START TIME**	09:30 arrival for a 10:00 start

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Opening Meeting Review of scope of inspection and inspection plan **Company Presentation** Overview of the company, the pharmacovigilance system and the quality system, including changes since the last inspection *(approx. 20 minutes)*	[redacted]	[redacted]
Receipt and review of documentation	-	Inspectors only
LUNCH	-	-

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Management of safety data Including but not limited to: • Transfer and clean up of Martindale data into the Ethypharm safety database	[redacted]	[redacted]
Document review	-	Inspectors only

MHRA INSPECTION NUMBER	TBC	**DAY**	2
PHARMACOVIGILANCE INSPECTION OF	Martindale Pharma/Ethypharm	**DATE**	10 July 2019
LOCATION	Building A2, Glory Park Glory Park Avenue Wooburn Green High Wycombe HP10 0DF	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Ongoing safety evaluation Including but not limited to: • Remedial signal detection activities and alignment with reference product information • Signal evaluation • Actions associated with updates to product information where required • Signal tracking	[redacted]	[redacted]
LUNCH	-	-

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Section 40	**Implementation of authorised product information** Specifically, maintenance of SPCs and PILs	[redacted]	[redacted]

MHRA INSPECTION NUMBER	TBC	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	Martindale Pharma/Ethypharm	**DATE**	11 July 2019
LOCATION	Building A2, Glory Park Glory Park Avenue Wooburn Green High Wycombe HP10 0DF	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Risk management activities Including but not limited to: • Tracking and oversight of risk management plan commitments, specifically additional pharmacovigilance activities and additional risk minimisation activities • Implementation of additional risk minimisation measures	[redacted]	[redacted]
Document review	-	Inspectors only
LUNCH	-	-
Document review	-	Inspectors only

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MHRA INSPECTION NUMBER	TBC	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	Martindale Pharma/Ethypharm	**DATE**	12 July 2019
LOCATION	Building A2, Glory Park Glory Park Avenue Wooburn Green High Wycombe HP10 0DF	**START TIME**	09:00

Purpose of Interview	**Session Lead**	**Staff to be interviewed**
Ad-hoc questions and queries	-	-
Document review	-	Inspectors only
LUNCH	-	-
Inspectors meeting	-	Inspectors only
Closing meeting	[redacted]	All welcome

[redacted]

Interviewees list:

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[redacted]

[redacted]

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