Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Ethypharm

MHRA Inspection Number: Insp GPvP 6934/17488-0004

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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

Inspection type:	Re-inspection at short notice
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:	06 November 2019
Lead Inspector:	[redacted]
Accompanying Inspector(s):	
Previous inspection date(s):	09-12 July 2019 05-09 February 2018, Martindale Pharma (now part of Ethypharm, reference number: Insp GPvP 156/2700-0047) 16 January & 22 February 2017 Viridian Pharma (now part of Martindale Pharma, reference number: INS/PHV/2017/004) 19 March-21 March 2012 Aurum Pharmaceuticals (as part of Martindale Pharma, reference number: Insp GPvP 12064/2700-0034) 19 March-20 March 2007 Martindale Pharma (Reference number: Insp GPvP 156/2700-0025)
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 Major finding 1 Minor finding
Date of first issue of report to MAH:	16 December 2019
Deadline for submission of responses by MAH:	22 January 2020
Date(s) of receipt of responses from MAH:	21 January 2020
Date of final version of report:	23 January 2020
Report author:	[redacted]

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Ethypharm was selected for reinspection at short notice as a result of the critical finding that was identified during the previous re-inspection performed on 09-12 July 2019. The purpose of the re-inspection was to determine if appropriate action had been taken as a result of the previous inspection. 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 a single pharmacovigilance system is operated by Ethypharm, encompassing Ethypharm, Martindale Pharma, Macarthys Laboratories, Aurum Pharmaceuticals and Viridian Pharma marketing authorisations.

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 focussed on a review of the systems and processes which were associated with the critical finding identified during the previous inspection in relation to risk management activities and was performed at Ethypharm UK's offices in High Wycombe, Buckinghamshire. Activities relating to the submission of safety variations following the July 2019 inspection were also reviewed following a referral to the GPvP inspectorate following the late submission of a safety variation to the MHRA since the inspection in July 2019.

The inspection was performed using interviews and document review (including evidence of corrective and preventative action deliverables). 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

Specific documents in relation to deliverables from the corrective and preventative actions from the July 2019 critical finding were requested by the inspection team on 04 November 2019 and provided by the company on the morning of the inspection.

B.4 Conduct of the inspection

The inspection was announced at short notice on 04 November 2019. The inspection was performed in accordance with the Inspection Plan.

A closing meeting was held to review the inspection findings at Glory Park, High Wycombe on 06 November 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 July 2019 there had been no significant changes to the pharmacovigilance system.

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

During the routine MHRA GPvP inspection of the Martindale pharmacovigilance system in February 2018, a critical finding was reported (CR.1) concerning deficiencies across the risk management system. During the re-inspection in July 2019, it was identified that Ethypharm had failed to adequately address elements of this finding, specifically:

CR1.a) Ethypharm had still not implemented the [redacted] educational programme. This programme was required to have been implemented prior to the UK launch of the product, which was in January 2017.

CR1.b) There were unacceptable delays to submit the RMP for [redacted] that was updated following the identification of discrepancies between two RMPs in place for [redacted] products reported as part of the February 2018 critical finding.

The critical finding was referred to the MHRA's Inspection Action Group (IAG), who issued a letter to Ethypharm stipulating specific immediate actions for the MAH to take regarding the implementation of the [redacted] educational programme.

During this subsequent re-inspection in November 2019, evidence was reviewed in relation to the corrective and preventative actions agreed following the July 2019 MHRA inspection, including those stipulated by the letter from IAG. This evidence was sufficient to assure inspectors that the above critical deficiencies reported earlier in the year following a failure to address the critical findings from 2018 for the risk management system had been resolved. Specifically, the evidence reviewed confirmed the following:

- Training of the sales team on the [redacted] educational programme
- Postal distribution of the educational materials to recipients in accordance with the approved distribution plan
- Tracking of the distribution of materials by the sales team in the Pathfinder customer relationship management (CRM) tool
- The upload of the educational materials to the UK electronic Medicines Compendium website (eMC)
- Written confirmation of the implementation of systems used by the main UK wholesalers, Alliance and AAH
- Submission of the updated [redacted]

Preventative actions proposed to the July 2019 inspection included the introduction and strengthening of the processes for ongoing governance and oversight of risk management activities. At the time of the inspection in November 2019, these were still at a nascent stage, however a minor finding and some comments have been raised for consideration in their development (please refer to sections C.4.3 and C.4.4).

C.4.2 Major findings

MA.1 Provision of information for supervision by the national competent authority

Requirements:

Part 16 Marketing Authorisations
Regulation 67(2) *"A UK marketing authorisation for a product which has been placed on the market ceases to be in force if the product to which it relates is not sold or supplied in the United Kingdom for a period of three years."*

Regulation 73(3) *"The holder of a UK marketing authorisation must notify the licensing authority if the product to which the authorisation relates is to be withdrawn from the market in the United Kingdom (whether temporarily or permanently)."*

Shortly prior to the inspection, intelligence was received by the GPvP inspectorate relating to the late submission of a safety variation to the MHRA since the inspection in July 2019, when a major finding in relation to delays in submitting safety variations was reported. During the investigation of this intelligence, the following non-compliance was identified.

Finding MA.1

Ethypharm had failed to notify the MHRA of the not-marketed status of [redacted] The MAH confirmed that the last batch of this product was released in 2015 and expired in 2017. No request for exemption to the 'sunset clause' was submitted by the MAH and therefore the UK marketing authorisation should have ceased to be valid from 2018.

The MHRA has published its interpretation of Article 23a and 24(4-6) of Directive 2001/EC regarding the 'sunset clause' which is available at:
https://www.gov.uk/government/publications/sunset-clause-request-for-public-health-exemption

This states in point 8 that "*The MA holder must report all cessations/interruptions to the MHRA.*"

Ethypharm confirmed that the licence was suspended in 2014 (20 October 2014) due to the presence of high molecular weight povidone following an Article 107i referral procedure, and that a new formulation was approved in 2015 (01 June 2015) but had never been marketed, however the not-marketed status was not notified to the MHRA, neither was a request for a public health exemption to the sunset clause.

In the response to this finding, Ethypharm should confirm and comment on the last date of release of product in light of the date the marketing authorisation was suspended.

Root Cause Analysis

[redacted]

[redacted]

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

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

C.4.3 Minor findings

MI.1 Risk minimisation measures

Finding MI.1 a)
There was no evidence to support that postal delivery failures for UK educational materials had been managed appropriately to ensure that all relevant healthcare professionals received the materials. There was a small number of posted hard-copy educational materials that were returned to sender ([redacted] had been received out of [redacted] posted in total, [redacted] ollowing the mailing that was completed on 31 August 2019. It was verbally explained that the validity of the contact details for these recipients, and whether they were legitimate targets for the dissemination, would be investigated by the sales team to ensure the distribution list was accurate, however the receipt of undelivered mail and any associated actions were not documented. This has been graded as minor due to the small proportion of undelivered mail. It was noted the company had not indicated any measures in written procedures or in the RMP to cover how indicators of effectiveness of the educational programme in the UK would be measured. Effectiveness measures in the RMP were limited to activities in France. Ethypharm should consider the approach to measuring effectiveness of the programme in terms of the extent of the implementation of the plan and its delivery (in accordance with GVP XVI.B.4.1) and propose in the next RMP update.
Root Cause Analysis
[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.4.4 Comments

1. It is acknowledged that the process for monitoring the implementation of the Espranor educational programme was still under development at the time of this re-inspection, with the updates to [redacted] 'Additional Risk Minimisation Measures implementation' (v4) still in draft and under the review and approval phase. On review of this draft, the following was noted:

   a) The draft SOP described how the RMP Working Party will monitor the implementation of the [redacted] educational programme through monthly meetings, which would include a review of the Educational Materials database (containing a list of recipients for the educational materials and the date of distribution to each), and a monthly output from the Pathfinder tool (used by sales team to track visits and distribution of materials), however it was noted that at the meetings held monthly since July 2019, a review of these specific outputs had not yet occurred.

   b) The preventative actions agreed for finding CR.1a in the July 2019 inspection report stated that the SOP would include an annex describing the Commercial Teams process(es), including for "The production and distributing the educational materials" and "Tracking the distribution of the educational materials". The draft procedure [redacted] did not include this content. Although the draft currently contained an appendix with an example of an additional risk minimisation measures (aRMM) tracker, the practical steps regarding its ongoing maintenance and use were not described within the procedure or appendix.

2. The customer relationship management (CRM) tool, Pathfinder, used by sale teams to track distribution of the [redacted] educational materials did not include the version of the materials distributed. Whilst there is currently only one version of the materials, it is recommended that the version is recorded to allow for appropriate future version control of the distributed materials in line with GVP XVI.B.6.

3. During the July 2019 inspection a major finding was reported in relation to failings in keeping product safety information up to date (MA.1). This included failures and delays to submit safety variations to update the safety sections of SmPCs and PILs for UK authorised products (MA.1b).

   Since the inspection, safety variations for six product licences were submitted to the MHRA, on the 23 August and 19 September 2019, prior to the submission of Ethypharm's initial responses to the inspection report.

   In the further assessment that was first submitted on 30 September 2019 in response to this inspection finding, Ethypharm stated:

   "Ethypharm checked if there is still products for which the SmPC has not been updated to include the concomitant use of [redacted] *and* [redacted] *and found out that all the variations were submitted."*

   It was confirmed by Ethypharm (during this November 2019 inspection) that these six safety variations were the result of an assessment conducted following the July 2019. In the interests of transparency, the extent of the actions taken after the July 2019 inspection should have been fully presented in the inspection responses.

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

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

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

D.2 Recommendations

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

APPENDIX I REFERENCE TEXTS

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

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	TBC	**DAY**	1
PHARMACOVIGILANCE INSPECTION OF	Ethypharm	**DATE**	06 November 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 status of the CAPA for the critical finding reported for the implementation of additional risk minimisation measures in July 2019.	[redacted]	All welcome
Receipt and review of documentation	-	
LUNCH	-	-
Document review, ad-hoc questions and queries	-	
Closing meeting	[redacted]	All welcome
N.B. Documents will be requested during the inspection. This inspection plan may need to be amended during the inspection. Inspectors: [redacted]		