Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GDP INSPECTION REPORT

WDA(H) 18716/9273505

ETHIGEN LIMITED

ISSUED BY:
Peter Brown
GDP Inspector

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Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

File Ref: **Insp GDP 18716/9273505-0006**
Inspection Date: **14/03/2017**
Company: **ETHIGEN LIMITED**

GDP Inspection Report

1. Report Reference no.:	Insp GDP 18716/9273505-0006

2. Inspected site(s) and contact details:

ETHIGEN LIMITED

ETHIGEN HOUSE
UNITS 10-16 COLVILLES PLACE
KELVIN INDUSTRIAL ESTATE
EAST KILBRIDE
GLASGOW
G75 0SN
UNITED KINGDOM

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3. Authorised operations:

- ☒ Procurement
- ☒ Holding
- ☒ Supply
- ☒ Export
- ☐ Brokering
- ☐ Other activities: (please specify)

4. Inspection date(s):	14/03/2017

5. Inspector(s):

Name(s) of the Inspector(s).

Peter Brown – **GDP Inspector, Lead Inspector**

Madeleine Ault – **Senior GDP Inspector, Accompanying Inspector**

MHRA

6. References:	Wholesale Distribution Authorisation Number or Registration Number of Broker: WDA(H) 18716

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7. Introduction:

Business Background

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WDA holder sharing site with [redacted] (manufacturing licence).
Centrally authorised product, UK product and [redacted] product procured from large and small wholesalers (some pharmacies with a WDA) for supply to pharmacies and wholesalers across the EEA.

Medicinal product with a marketing authorisation elsewhere in the EEA is procured and contracted to [redacted] fro parallel import manufacturing activity before being re-returned to Ethigen for onward supply.

This inspection was triggered due to large volumes of [redacted] being sold to customers unlikely to use this quantity legitimately.

Review of WDA(H)

MEDICINAL PRODUCTS

☒ with a Marketing Authorisation in EEA country(s)

☒ without a Marketing Authorisation in the EEA and intended for EEA market*

☐ without a Marketing Authorisation in the EEA and intended for exportation

Medicinal products with additional requirements

☒ Products according to Art. 83 of 2001/83/EC

- ☒ Narcotic or psychotropic products
- ☒ Medicinal products derived from blood
- ☒ Immunological medicinal products
- ☐ Radiopharmaceuticals (including radionuclide kits)

☐ Medicinal gases

☒ Cold chain products (requiring low temperature handling)

☒ Other products: (please specify here or make a reference to Annex 5)
4.7 Products without a Marketing Authorisation in the EEA and intended for exportation

Date of previous inspection:

Name(s) of Inspector(s) involved in previous inspection: Ewan Norton

Date of last inspection: Feb 2016

Overview of inspection findings from last inspection and the corrective action taken:

N/A – GMP Licence

Major changes since the previous inspection:

Recent changes to transport providers including increased volume of work to [redacted] and move to temperature controlled vehicles from January 2017 for all non UK and non [redacted] incoming deliveries that are the responsibility of Ethigen.

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New heating installed 2013

8. Scope of Inspection:
For cause inspection assessing compliance with the Guidelines of 5 November 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01) and the Human Medicines Regulations 2012 as amended.
9. Inspected activities:
GDP Inspection of all GDP activities, operations, records and documentation under the licence pertaining to this site; Procurement, Holding, Supply, Export.
10. Activities not inspected:
None.
11. Personnel met during the inspection:
[redacted]
12. Inspectors findings and observations relevant to the inspection and deficiencies:

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- **Quality Management**

  A Quality Management System was in place, consisting of a number of version controlled and dated standard operating procedures (SOPs). These were either written by, peer reviewed by or approved by the RP in accordance with the Document Control [redacted]

  Deviation management and CAPA system was in place described in [redacted] Service Level Failures and Non-Conformance Reports. It was noted this had not been utilised (either as SLF, NC or CAPA) to capture a number of deviations regarding operations and premises issues, noted during the course of the inspection.

  A change control process, [redacted] was in place, however this had not been utilised to control significant changes to operations, such as the recent changes to ensure abnormal sales patterns are monitored and the imminent change of courier from [redacted]

  Management review process described in [redacted] Quality Management Meetings and Review

  Processes in place to address quality risk management, [redacted] had not been effective in identifying high risks and resolving risk, e.g. warehouse roof leaks.

- **Personnel**

  Staff training records were reviewed and found to be acceptable. Sales staff had specific training around notification of unusual sales patterns to senior staff, from December 2016. There was evidence of refresher training provided.

  Questionnaires and ongoing follow-up assessments were utilised to ensure the effectiveness of training.

  Training practices were defined in [redacted]

  The responsibilities of the Responsible Person (R.P) were not defined in writing.

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There was a lack of detail surrounding the delegation of duties of the R.P to deputy R.Ps. For example responsibility for training.

It was noted some key staff, for example [redacted] and [redacted] had no record of falsified medicines awareness training.

Sales, goods in, damages and returns staff were interviewed by the Inspectors and found to be competent and knowledgeable in areas discussed.

- **Premises and Equipment**

The site security consisted of 36 CCTV cameras both internally and externally. 24 hour security patrols around the site area. An alarm system was in place to secure the premises.

Access to the building and separate zones was controlled by way of key card restricted access. Additionally, security personnel only release controlled drug storage area keys to authorised staff. A list of these approved staff was noted on site.

Warehouse separated into several zones:

Import area (where import relates to procurement from EEA). Stock batch checked and outer boxes labelled for storage in the bulk storage area. The disposition of these is controlled by the buyers. All products stored together until disposition, including to [redacted] Discrepancies are photographed and logged before being raised with the buyer.

Goods in area. Process was followed through and showed prioritisation of cold chain and CDs as these details are identified on master product details. Some times of receipt of delivery had not been recorded. . Some staff unfamiliar with the identification of THR medicines, although on the licence and stocked (e.g. seen [redacted]. The area included a caged and locked quarantine area. History of several items investigated and found to be controlled adequately.

Dispatch area. Tote bins and boxes are transferred through to the area for inclusion on individual vehicle runs. These are identified on the labels.

Picking warehouse. The area contains the two Home Office approved walk-in CD bulk stores with controlled access. A further CD walk-in storage area is located in a different part of this zone; this is also controlled access and carries [redacted] etc as well as a damages location [redacted] x [redacted] The picking areas have bulk locations and pick faces, including some gravity-fed. Picking is with voice recognition software. One small area of a few square metres was found to contain three damaged products that had not been segregated. Caged area (newly installed) for storage of [redacted] and other products with a high 'street value' This had been the old [redacted] area. Some tote bins containing water from a roof leak were seen. These were positioned over stored stock. Redundant heating appliance now disconnected.

[redacted] area completely segregated and currently not in operation.

Bulk storage locations. See photos attached on next page. Puddles of water were seen in two locations (OK 23 and OK 36) with one area showing staining (OJ35). Some wooden pallets were wet at the base (OJ23 and OK 35) although no evidence of wet stock apart from a few drops on the outer shrink wrap of the pallet in location OK21 (one of two retrieved by fork lift at inspector's request). The bulk storage area slso contained some stock from [redacted] marked as QP released.

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[redacted]

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Export warehouse. This area contained bulk and pick locations. There was a caged area for products with a high street value. A further caged area was divided into two areas, one used for customer returns and one for warehouse products removed from location for follow-up e.g. due to damage, date etc. Packing area included several consignments awaiting completion or shipment. One of these was to [redacted] in [redacted] although this customer had still not been approved. A further tote bin containing water was found.

A temperature mapping exercise had been completed 12/12/16 through to 20/01/17 using calibrated Thermistor dataloggers in each area (ambient and cold chain) for one week. This had been done following [redacted] Validation of cold rooms and premises for temperature monitoring and mapping. This detailed steps taken to assure the suitability of the premises, data and calibration. Although generally acceptable, there was no detail within the conclusion recommending or confirming monitor placement, nor a suggested re-validation period. This differed significantly from the detail in the summer 2015 mapping exercise.

Cold chain facilities consisted of two cold store rooms, with one defined as "export fridge". Both rooms were serviced by a cooling unit, designed to keep the temperature at a certain level. The fridges were equipped with audio and visual alarms [redacted] with acceptable limits set at 2 – 8 degrees Celsius as defined in [redacted] Refrigeration Failure. The acceptable temperature range was described as 2-8C but there was allowance for excursions which had not been quantified or justified. It was noted one of the calibrated thermometers reached a reading of 7.9; the R.P was advised to consider limit variations to protect stock integrity.

Cleaning procedure [redacted] in place although some pallets had high levels of dust.

Warehouse heated via gas appliances. Pest control contract in place (not inspected) and controlled through [redacted] Pest Control. Waste management contract in place and segregation and documentation of waste seen throughout controlled by [redacted]

Validation of computer systems not inspected and description of computer system not requested..

- **Documentation**

Documentation was defined as being stored for 5 years, and was archived on site within the warehouse.

Stock management was controlled via the [redacted]

Temperature records were available for inspection and found to be in order.

Sales and procurement records were available as requested by inspectors.

Documentation was version and number controlled, as defined in [redacted] as well as authorised by either R.P or Deputy R.P.

- **Operations**

A qualification procedure was in place, detailing actions and activities prior to commencement of supply. Annual re-checks of customers and suppliers were described within the SOP. There were no checks against the suspended and terminated lists. A proposed project to amend stock management and sales software was ongoing to assist with the restriction of stock supply to non-entitled customers.

A reference to control measures regarding sales order diligence was in place.

Periodic re-checks of entities were described within the procedure, including authorisations against EudraGMDP and the MHRA or other competent authorities as appropriate.

Although there was no reference to checks against the MHRA suspended and terminated lists, the Inspectors accepted that there was evidence that the activity was taking place, authorised by the R.P.

A monitoring of lines considered at risk of abuse, including controlled drugs and [redacted] was in place. Evidence of regular review was available for inspection. These assessments were made by the managing

director, who had experience with prescribing patterns. There was no method to review large orders prior to despatch and decisions were made retrospectively.

Records of customer qualification on hand were well documented, including Home Office Licence checks. There was some historic transactions of concern observed, however none since MHRA liaison.

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Warehouse incoming goods processes were inspected. It was unclear as to how the company ascertains the temperature of product. An inspected receipt from supplier [redacted] appeared to contain some temperature deviations.

Documentation despatched with products was to an acceptable standard.

Supplier and customer documentation reviewed were acceptable.

General operations of procurement, receipt, holding and supply were reflective of processes described in procedure and were acceptable.

One consignment was seen in the export area destined for 8pm chemist. This had some large quantities of products typically wholesaled. Although the company no longer hold a WDA, they are an internet pharmacy..

Processes for the management and handling of controlled drugs were acceptable.

- **Complaints, Returns, Suspected Falsified Medicinal Products and Recalls**

A complaints procedure [redacted] Procedure for customer complaints) was in place, defining actions to be taken upon the receipt of a quality complaint. Although this considered the MHRA, it was noted that there was no wider consideration of notification to foreign sovereign competent authorities where product had been sourced from abroad.

Falsified medicines awareness was defined by way of procedure and appeared adequate. Mechanisms were in place to notify the competent authority.

A recall procedure was in place, defining activities and responsibilities, including a definition of class of recalls. There was provision for a mock exercise in lieu of a live exercise. A recent live recall exercise had been conducted and was found to be satisfactory.

The returns process was examined and found to be acceptable, with defined devolved duties. Sentencing was acceptable. Segregated areas defined and process demonstrated adherence with written procedure. One member of staff routinely in this area [redacted] with further trained staff [redacted] available if required. All training records seen.

- **Outsourced Activities**

Incoming transport outsourced to Freshways, [redacted] and [redacted] Agreements reviewed. The company have proposed transferring from [redacted]. A draft agreement is being worked on and test runs are to be used in the next few weeks. This had not been covered by a change control process. A process was in draft to conduct desk-top audits of these.

- **Self-Inspection**

Self-inspection functions were defined via [redacted], conducted annually and recorded via form [redacted] Records of previous inspections were available for inspection and found to be acceptable.

- **Transportation**

Incoming transport in temperature controlled vehicles from EEA is contracted to [redacted] and [redacted] rest of EEA). Expectation is 2-8C and 15-25C for both. Incoming delivery documentation for Freshways was seen to state +4C on the delivery documentation but carried temperature printoouts showing temperatures ranging between 3 and 13C. This had been approved without any evidence that the stock could acceptably be transported at these temperatures. Full temperature control of these EEA incoming deliveries has been in place since January 2017.

Incoming transport from parts of the UK is done by own drivers using own vehicles, typically [redacted] and [redacted] Drivers collect from and deliver to Northern areas with approx. 12 drivers based at this site, 8 in

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Manchester and Bolton, 1 in Newcastle, 1 in Birmingham and 5 in Northern Ireland. These operate from unlicensed depots/hubs belonging to other companies and staff are managed by logistic managers based in East Kilbride and supervisor drivers based at the hubs. A 'hub run' leaves here at 12.30am returning late morning. Further inspection of these activities not done on this occasion.

Incoming transport from UK and [redacted] is contracted to [redacted] (next day delivery service) with an imminent switch to [redacted] on a phased basis. Several items were logged and the supplier qualification details were checked. Some of these packages were customer returns.

A risk assessment had not been done for clandestine travellers; although no evidence of these had been found, the company is at risk as shipments are arriving on a regular basis by road from elsewhere in the EEA.

A cool box validation had been done for cold chain products travelling to and from Ethigen to addresses within UK and [redacted] The conclusion did not describe the approved period of time these had been validated for and under what external conditions. The risk of freezing and the risk of one low temperature (2.1C) had not been discussed in the conclusion.

Assurance of ambient temperatures in transit within the UK and [redacted] was addressed by placing a datalogger in incoming and outbound consignments on a weekly basis. The results were collated but not adequately analysed and concluded . For example a large number of temperatures were logged as below 8C and also below 2C without consideration as to whether the loads contained products labelled as 'do not refrigerate' or 'do not freeze'. E.g. 1.9C 11/01/17 and 0.8 to 1.9C for over 3 hours 12/01/17. Conclusions were not, therefore, available to be carried through to routine practices.

- **Specific Provisions for Brokers**

  Not applicable to business model.

13. Other specific issues identified:
None.
14. Miscellaneous:
None.
15. Annexes attached:
N/A

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16. List of Deficiencies classified into critical, major and others:

1. CRITICAL

None observed.

2. MAJOR

2.1 Export activities were deficient, in that:

2.1.1 No defined process was in place to cover licence provisions export 2.4 or introduction for export 4.7 to customers in third countries.

2.1.2 There was no ability to electronically segregate unlicenced imported product intended for third countries from inventory destined for EEA markets.

EU GDP Chapter 5, sub-section 5.2, 5.3 & 5.5

2.2 Premises and equipment were deficient, in that:

2.2.1 There was evidence of water damage, indicative of a long term issue, located close to inventory.

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2.2.2 Some wooden pallet bases were noted to be damp during the inspection.

2.2.3 [redacted], Refrigeration Failure, states temperature excursions of cold chain inventory was permitted however there was no definition or justification of this activity.

2.2.4 The recent temperature mapping exercise did not detail the recommended placement of monitors in its conclusion, nor suggest a re-validation date of the exercise.

2.2.5 There was some evidence of damaged medicines that had not been withdrawn from the saleable stock area.

2.2.6 There were noticeable levels of dust on various pallet spaces.

EU GDP Chapters1 & 3, sub-section 1.4, 3.2, 3.3.2

2.3 Personnel practices were deficient, in that:

2.3.1 There was a lack of detail of R.P duty delegation to deputy R.Ps.

2.3.2 There was no definition as to the responsibilities of the R.P.

2.3.3 Some key members of logistics staff within the goods in team had no record of conducted falsified medicines training.

2.3.4 There was no documented training detailing the management of THR inventory or identification of PA licenced medication.

EU GDP Chapter 2, sub-section 2.2, 2.4

2.4 The transport validation exercise for both ambient and cold chain inventory was deficient, in that:

2.4.1 There was no consideration of temperature excursions; for example, recorded temperatures of between 0.8 and 1.9 degrees Celsius on the ambient validation for 12/01/2017.

2.4.2 There was no consideration of products labelled “do not refrigerate” and “do not freeze”.

2.4.3 The exercise lacked adequate conclusion and did not consider the length of time cold chain packing had been validated for relative to external conditions.

2.4.4 There was no consideration of a low recorded of 2.1 degrees Celsius in the cold chain validation and the potential impact of freezing of the product.

2.4.5 The validation did not summarise all the tests completed during the reviewed conclusion. For example vehicles used, packaging, datalogger placement and repeated access to the vehicle.

EU GDP Chapter 9, sub-section 9.2, 9.3, 9.4

3. OTHER

3.1 Supplier and customer qualification activities were deficient, in that:

3.1.1 There was no procedurally defined reference to checks against the MHRA suspended and terminated lists.

3.1.2 The current process did not include third country supplier or customer qualification.

EU GDP Chapter 5, sub-section 5.2, 5.3, 5.5

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3.2 The Quality Management System was deficient, in that:

3.2.1 No change control had been utilised to implement the changes to sales ordering pattern monitoring in accordance with [redacted] nor control the imminent change from [redacted] Couriers.

3.2.2 No non-conformances had been raised to record deviations for one example of received stock out of temperature (defined as +4C, readings below 4 and above 12/13), or warehouse leaks observed during inspection.

3.2.3 Risk Assessment form FMEA had not been completed to address noted deviations or significant changes designed to address risks, as per [redacted] nor non-conformance reports or CAPA initiated.

3.2.4 The risk register had not been updated to consider the above risks.

EU GDP Chapter 1, sub-section 1.2, 1.4

3.3 The complaints procedure did not consider wider notification to foreign sovereign competent authorities where product had been sourced from outside the UK.

EU GDP Chapter 6, sub-section 6.2

17. Inspectors' Comments:
Some documentation, such as the outdated recall alert notification link within [redacted] was incorrect. Appropriate fridge temperature alarm limits were discussed with the R.P to assist in the protection of stock. The risk of clandestine travellers had not been considered within the risk register process. This should be considered; it was noted that there had been no incidents of this occurring to date.
18. Recommendations:

Continued support of your wholesale dealer's authorisation (WDA(H) 18716) pursuant to Regulation 18 of the Human Medicines Regulations 2012 [SI 2012/1916] (a "wholesale dealer's licence") will be recommended to the licensing authority.

Site and authorisation pursuant to Regulation 18 of the Human Medicines Regulations 2012 [SI 2012/1916] (a "wholesale dealer's licence") will next be inspected as part of the MHRA's risk-based inspection programme, the frequency of inspection being determined by the nature of the activities the licence holder undertakes and previous compliance history. The risk profile of a company may change over time and consequently provisional re-inspection dates given in this report may change".

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The provisional date for the next inspection of this site is [redacted]

19. Summary and conclusions:

[redacted]

20. The inspection report should be signed and dated by the Lead Inspector:
Name: Peter Brown **Signature:** [redacted] **Organisation:** MHRA **Date:** 14/03/2017 [redacted]

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