Medicines & Healthcare products Regulatory Agency

MHRA

INSPECTION REPORT

WE PHARMA LIMITED

UNIT 6

7 & 30 (C/O THE LIGHTBOX)

111 POWER ROAD

LONDON

W4 5PY

UNITED KINGDOM

Head Office:
Inspection, Enforcement & Standards Division, MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU

United Kingdom

Telephone: 020 3080 6000
Email: info@mhra.gov.uk

Section A Inspection Report Summary

Inspection requested by: License variation to add secondary packaging.

Scope of Inspection: Full inspection against MS, WDA(H), new WDA (V) and secondary packing

Licence or Reference Number: MS34868

Licence Holder/Applicant: WE Pharma Ltd

Details of Product(s)/ Clinical trials/Studies:

Activities carried out by company:	Y/N
Manufacture of Active Ingredients	N
Manufacture of Finished Medicinal Products – Non sterile	N
Manufacture of Finished Medicinal Products - Sterile	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	N
Packaging – Secondary	Y
Importing	N
Laboratory Testing	N
Batch Certification and Batch Release	N
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *Specials, import of unlicensed and secondary packaging.*	

Name and Address of site(s) inspected (if different to cover):

WE PHARMA LIMITED
UNIT 6
7 & 30 (C/O THE LIGHTBOX)
111 POWER ROAD
LONDON
W4 5PY
UNITED KINGDOM

Section 40

Site Contact: [redacted]

Date(s) of Inspection: 31/07/2018

Lead Inspector: [redacted]

Accompanying Inspector(s): None, but accompanied by [redacted] on induction.

Case Folder References: Insp GMP 34868/13177435-0005

Section B General Introduction

B1 Background information

Section 43

The inspection was prompted by a variation to add secondary packaging to the MS license. However, a follow up inspection following the initial grant of the MS was overdue. The company has a focus on Expanded Access Programs (EAP), Named Patient Programs, Clinical Trial Sourcing and Reference Product Supply. The UK headquarters of WEP Clinical were established in London in 2008 and the US headquarters were later established in North Carolina in 2012 (run by a family member). The company had also applied for a WDA(V) and were varying the WDA(H). The site is a series of rented units in a managed facility known as the [redacted] Multiple site numbers had been used although the company were effectively a single site. Post inspection this was rationalised to site 13177435. Specials were predominantly supplied to hospitals in [redacted] due to demand for unlicensed products for specials clinical needs and lack of availability of such in these countries. There were no current plans for relabelling Vet specials and the company were advised this would need a ManSA.

Previous Inspection Date(s): 3rd December 2015

Previous Inspectors: [redacted]

B2 Inspected Areas

Review status of licences & site master file – variation to MS, new WDA(V), change of addresses WDA(H).
Secondary packaging proposals
Units/site numbers to be rationalised
Supplier assessment unlicensed imports from outside EEA.
Special clinical needs
Confirmation of bona fides (suppliers and customers)
Import notice management
Review of Defect Reports & Recalls systems
Customer Complaint records systems
Deviations/Investigation reports systems
Reworks systems
Management quality review
Procedures and Document control
WDA(V) systems & knowledge
Site inspection:
Goods receipt, checking, product batching and storage of packed stock
Components storage, sampling and release
Own label printing
Own Leaflet printing

Packing & Labelling Operations
Line clearance
Area logs/status/planned ways of working
Control of Cold Chain Supply/receipt
Falsified product checks
Batch docs preparation
Artwork control
Artwork specifications
Batch Document and logs review
Finished batch release
Distribution
Training Records
Technical/contract Agreements
PPM, Calibration, Service contracts and change control for fridge/freezers
Self-inspection plan

Limitations / exclusions to inspected areas

None

Section 40

B3 Key Personnel met/contacted during the inspection

[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	V1 draft (not dated)	Y/N
Compliance Report	5/7/18	Y
Comments:		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes are recorded in the pre-inspection compliance reports held in the case folder.

Changes since previous inspection which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

Application for secondary packing and WDA (V)

Future planned changes which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

New warehouse area, unit 12, potential future transfer of secondary packing to this area.

Site numbers rationalised to single number under 13177435

C2 Action taken since the last inspection

CAPA completed.

C3 Starting Materials

General

There were no starting materials as such other than blank labels used for the printing of over labels. The procurement of these was not reviewed.

Compliance with TSE Guidelines

Certification obtained for unlicensed imports.

API Compliance

N/A

C4 Pharmaceutical Quality System

The procedure for deviations/non-conformances was reviewed and found generally acceptable however the execution of the procedure was not adequate, and a deficiency was recorded

The change control system was not specifically reviewed however, it was noted that the change control for introduction of the new packing activity did not include an adequate post change review.

Section 43

Product seen in the warehouse unit was queried with the site in terms of controls;

[redacted] writing pack for [redacted] g had been sourced as a 3rd country specials import; however, the supplier qualification was not considered adequate.

Similarly, a batch of bottle packs of [redacted], [redacted] were unusual in that they were labelled with plain white labels with details in black type but containing no artwork or license numbers. The consideration of the controls used for manufacture of an unlicensed product in [redacted] had not been considered and reliance was placed on an EU GMP certificate (from 2010 and 2013 in the supplier qualification pack) that may not have covered the facility, equipment and systems used for the production/packing. The [redacted] had been approved by MHRA but carried a restriction that it must not be supplied to UK markets. The site did not have an adequate system for ensuring that such restrictions were applied and enforced. The company's control over import approval requests and tally of import against approvals appeared adequate.

Deviations [redacted] were reviewed and deficiencies recorded.

Section 43

[redacted] related to a decision by the company to forward labels to their customer to over label with extended expiry date. The product [redacted] was owned by [redacted] and had been manufactured at [redacted] and labelled at [redacted]. The product owner, for which WEP was acting as EU distributor, had requested that the labels be sent with stock to provide an option of an extended expiry. WEP had not challenged this request which was related to an Expanded Access program and had not considered the need to have it labelled in a controlled manner. WEP did not receive any data to justify the extension. WEP still had stock of the batch and the labels and needed to regularise this activity.

Customer approval appeared generally adequate with most specials being supplied to hospitals. Some e.g. [redacted] required confirmation of orders from the local regulator Infarmed.

A guide had been developed of the terminology and expectations for veterinary medicines and this appeared demonstrate an adequate grasp of requirements.

C5 Personnel

The organisation diagram in the SMF was not reflecting the Quality Management organisation adequately and needed to be revised.

C6 Premises and Equipment

The facilities used by WEP were Unit [redacted] (admin, unit [redacted] (admin and new small secondary packing room), Unit [redacted] warehouse and distribution. The site was planning to convert a recently leased unit [redacted] as a new larger warehouse which they hoped to be ready by [redacted] Following successful transfer to unit [redacted] unit [redacted] would be decommissioned. Change control [redacted] applied to the new packing room. This was a small room within Unit [redacted] that had been set up with a packing table, printer/PC and temperature monitoring. The door was locked with the key access restricted and as such was regarded as a controlled area. It was fit for purpose for the very basis level of activity proposed.

C7 Documentation

The company were now using SharePoint for retention and management of documents with documents signed using e signatures (DocuSign). The batch record format proposed appeared adequate.

C8 Production

Secondary packaging was to be limited to over label on to the carton and a PIL replacement, with English language translated text from the original documents/packs. A low throughput was initially expected with around 5-10 packs relabelled per week.

Several issues were recorded with the systems in place for secondary packing, see the deficiencies.

The site had conducted packing operations on two 'mock' packs to test the system and demonstrate the process to the inspector. This highlighted a few points for development recorded as deficiencies.

C9 Quality Control

N/A

C10 Outsourced Activities

Outsourcing was used for translation of cartons and PIL text. Artwork would be outsourced for translation and a PDF received back from the contractor. This would be checked following transcription into an excel spreadsheet before returning to PDF as an available document. This appeared cumbersome with risks of errors in the transcription step given the nature of the data being transcribed. The site was advised to carefully review all process in use to ensure they remain fit for purpose.

C11 Complaints and Product Recall

The complaint and recall procedures were generally acceptable however, the investigation and correction of complaints was deficient and the real time recording, and reporting of recalls was not adequate. Safety events were required to be reported to MHRA via the yellow card scheme although none had been reported to date.

Section 43

Complaints [redacted] were reviewed and deficiencies recorded.

A recent recall of [redacted] imaging agent triggered by the [redacted] was reviewed.

C12 Self Inspection

Self-audit was being conducted related to current activities but there were no plans to amend this for the new packaging activity.

C13 Distribution and shipment (including WDA activities if relevant)

The company processed around [redacted] shipments per day with ambient goods having no temperature control and cold chain being packed into temperature control boxes (the validation was not reviewed).

C14 Questions raised by the Assessors in relation to the assessment of a marketing authorisation

None

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

D1 Critical

None

D2 Major

2.1	Management of deviations, complaints and resulting CAPA was deficient in that:
2.1.1	There was not adequate detail recorded in temperature deviation [redacted] to provide a clear explanation of the issue.
2.1.2	[redacted] did not include an adequate evidence file to support acceptance of returned [redacted] product for reshipment in that there was no information recorded of the specific shipment conditions

Section 43

to/from [redacted] and no fact-based risk assessment to support the decision.

2.1.3 The CAPA for the complaint [redacted] (supplied as [redacted] did not included updating the incoming goods procedure with the required check.

2.1.4 The complaint [redacted] related to the product supplied by the [redacted] as non-sterile rather than sterile, did not consider other supplied products similarly at risk of order/supply mix up.

2.1.4.1 The complaint [redacted] for delivery of [redacted] outside the transport validated window did not include CAPA action taken on the material supplied.

EU GMP C1.4(xiv), C1.8(xi)

2.2 The supply of product with updated labels extending the expiry date was inadequate in that:

2.2.1 WE Pharma supplied labels with the product to a customer under the specials license for the customer to affix the labels to reflect a change of expiry of a product for expanded access without considering the need to have the product relabelled in a controlled manner. In doing so they inappropriately transferred the licensable manufacturing step to the customer.
The Human Medicines Regulations 2012 (as amended) SI 2012/1916. Part 3, regulation 17(1)

2.3 Supplier Assessment and approval was deficient in that:

2.3.1 There was not adequate evidence held of the suitability of the [redacted] supplier in [redacted]. Although a GMP certificate of the manufacturing site was held, the product appeared to be an unlicensed hand packed product for which there appeared to be no evidence to confirm that the manufacture had occurred under systems and facilities subject to the EU GMP certification.

2.3.2 Neither the original or re-qualification of the [redacted] supplier for [redacted] included evidence of suitability of the product (manufactured by [redacted] An extract from [redacted] indicating the sources was a [redacted] licensed product was only printed during the inspection.

2.3.3 There had not been an adequate assessment conducted of the translation provider [redacted]' with only a basic questionnaire and ISO certificates provided. The assessment did not challenge or clarify actual performance of the company or consider which language translations the company were proposing to provide. There were no plans for ongoing assessment of the effectiveness of the supplier.

EU GMP C7.5, C7.7, C7.8
EU GDP 5.2

D3 Others

3.1 The proposed Secondary packaging processes were deficient in that:

Section 40

3.1.1	The packing guide referred to the Responsible Person oversight of the process rather than the Quality Controller required under the MS license.
3.1.2	The process document did not state that required checks were to be by a second person
3.1.3	The proposed [redacted] included an option for a carton to be supplied yet the company had confirmed they did not intend to change cartons.
3.1.4	The picking for packing process referred to/used the QNE /disposal process which was not relevant for picking for packing manufacturing process.
3.1.5	The mock up batches had production approval recorded by the person who had repacked the mock batch and thus this was not an independent check.
3.1.6	The mock up batches were reviewed/released by the person who had approved the labels and thus this was not a fully independent release.
EU GMP	C1.8(iv), C4.21(i) The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials MHRA Guidance for 'Specials' Manufacturers https://www.gov.uk/government/publications/guidance-for-specials-manufacturers 3.1.6
3.2	There was no system to ensure import restrictions placed by MHRA were applied e.g. not for supply in UK, due to presence of potential licensed equivalents. The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials 5.2(2)
3.3	The inspector observed an example of import occurring before approval was received from MHRA e.g. betadine from the [redacted] subsidiary. The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials 5.2(3)
3.4	There was no record of conducting checks for falsified products on receipt.
EU GDP	6.4
3.5	There were no plans in place for post change implementation reviews or for self-audit of the secondary packing process.
EU GMP	C1.4(xiii), C1.4(xvii)

3.6 Recall records were deficient in that:

3.6.1 There was not a contemporaneous record for stepwise progress and key times/dates. A summary report had not been issued against the recent recall.

EU GMP C4.8, C8.29

D4 Comments

4.1 The inspector noted the inconsistent application of risk-based controls by the site as there had been temperature loggers introduced with ambient product through movement on site yet there was no temperature monitoring in the higher risk process of distribution.

Section 43

4.2 Warehouse segregation may not be adequate to prevent mix of stock and inadvertent supply to wrong 'markets'. The company should consider how restrictions on supply could be controlled within the [redacted] system.

4.3 The inspector noted the multiple site numbers in place and undertook to review this with the Process Licensing team with a view to agreeing a single site number for future use. Post inspection, this has been completed and a single site number 13177435 will be present on licenses in future. Any additional units added in future from the same address will result in retention of this site number and amendment of the site name to add the new unit number.

4.4 The inspector noted the proposed future warehouse capability via Unit [redacted] and requests the site to advise once that unit is refurbished and ready for use. The unit should not be used prior to approval by MHRA and will require a variation to add this to the site identification.

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme	✓	[redacted]	
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

Attended by those identified in B3, commitment given to corrective action.

F2 Assessment of response(s) to inspection report

Final response following RFI 3 received on 4th September.

F3 Documents or Samples taken

None

F4 Final Conclusion/Recommendation, Comments and Evaluation of Compliance with GMP and GDP

The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
Directive 2001/83/EC, Directive(s) 2003/94/EC and 2011/62/EU	
GMP as required by HMR 2012 (as amended)	√
Directive 2001/20/EC	
Directive 2001/82/EC	
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	√

and is acceptable for the products in question.

Section 40

Name and Dated Signature of Inspector (s):

Signed: [redacted]

Dated: 10/09/2018

Accompanying Inspector: **N/A** **Dated:**

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	3	Last inspection:	0
Other deficiencies this inspection:	6	Last Inspection:	4

Section 43

(b). Provisional Rating based on Inspection Output (✓ applicable box)

Risk rating level	Input from current Inspection Findings (last inspection findings applicable to rating V only)	Provisional rating – this assessment	Final rating last assessment
0	Serious triggers outside the inspection cycle	[redacted]	
I	Critical finding		
II	>/= 6 Major findings		
III	<6 Major findings		
IV	No critical or Major findings		
V	No critical or Major findings from current or previous inspection and <6 other findings on each.		

(c). Risk Assessment Inputs – discriminatory factors (✓applicable box)

[redacted]	None relevant (default)
	Significant concern over robustness of quality system to retain adequate control
	Significant failures to complete actions to close previous deficiencies raised at the last inspection
	Complex site
	Significant changes reported in Compliance Report
	Significant mitigating factors applied by the site
	Higher risk rating identified by other GxP and considered relevant to the GMP site
	Relevant site cause recalls, notifications to DMRC or rapid alerts since last inspection
	Nature of batch specific variations submitted since the last inspection give concern over the level of control
	Regulatory action related to the site
	Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments from post inspection action plan
	First Inspection by MHRA (does not require counter-signature for RR II)
	Other discriminatory factor (record details and justify below)

(d). Inspectors Comments Related to Discriminatory Factors

Inspect as per deficiencies

(e). Risk Rating Result Incorporating Discriminatory factors (✓ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

Section 43

(f). Basis for risk-based acceptance of specific matters arising during the inspection

[redacted]

(g)
noted in section (f) above

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments (Risk rating level 0, I, II):

[redacted]

Section 43

[redacted]

(j). Confirm Agreed Risk rating following this inspection:

Risk Rating:	Next Inspection target date:
[redacted]	

Notes regarding re-inspection and GMP certificate validity

1. The inspection schedule is based upon risk and resource. This date may change at any time due to factors not pertaining to your site.
2. The GMP certificate does not 'expire' it is provisionally assigned 3 year validity date. For external questions regarding your validity thereafter; please advise that this can be confirmed by contacting the inspectorate at gmpinspectorate@mhra.gov.uk