Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Syri Limited
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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA / MS 39307

Licence Holder/Applicant: SYRI 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	Y
Manufacture of Finished Medicinal Products - Sterile	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	Y
Packaging - Secondary	Y
Importing	Y
Laboratory Testing	Y
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *SPECIALS*	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 09Jun2021 to 10Jun2021

Lead Inspector: [redacted]

Accompanying Inspector(s): N/A

Case Folder References: Insp GMP 39307/303632-0048

Section B General Introduction

B1 Background information

Syri Limited is part of the B&S Group and markets products under the Thame Laboratories trading style. This company is located at the Bradfield Road, Ruislip site. Another company in the B&S group, [redacted] conducts PLPI activities at this site. The PLPI activities were not included within the scope of this inspection. Syri Ltd hold a WDA(H) which is only used for distribution of products to other parts of the B&S group. WDA(H) activities are inspected separately by the MHRA GDP team. The company advised that PLPI activities were not conducted under the Syri licence.

Not all buildings associated with this site were in use in respect to the activities being inspected with other licences held by the same parent group using these facilities.

Previous Inspection Date(s): 29Oct2019 to 30Oct2019

Previous Inspectors: [redacted]

B2 Inspected Areas

Quality management Systems
Deviations; Investigations; CAPA; OOS/OOT; PQR; Change Control; Validation; Data Integrity and Data Governance; Documentation; BMR Review; Stability; Capacity Planning; Recall; Environmental Monitoring
Site Tour
Warehousing; Manufacturing (MS & MIA); QC Chemistry; QC Microbiology

Limitations / exclusions to inspected areas

WDA activities were not inspected

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted] (MIA)	Y
Compliance Report	07Jun2021	Y
Comments: None		

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:

- Reduction of licenced batches manufactured from [redacted] to [redacted] batches/month
- Continuous temperature monitoring introduced across site

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

- [redacted] under construction

C2 Action taken since the last inspection

Actions taken were in broad compliance with the commitments made

C3 Starting Materials

General

The supplier approval procedure ([redacted] was reviewed without comment.

Compliance with TSE Guidelines

Acceptable TSE statements were included in the supplier approval status for all products reviewed.

API Compliance

Not reviewed at this inspection

C4 Pharmaceutical Quality System

A selection of deviations with associated CAPA were reviewed:

- [redacted] concerning a water leak from PW system point [redacted] (Specials area)
- [redacted] in respect to [redacted] manufactured under change control
- [redacted] concerning a site wide power outage (14Feb2021)

- [redacted] concerning the transcription of a damaged BMR
- [redacted] in respect to an OOS for [redacted] assay
- [redacted] concerning the inadvertent use of a non-authorised material in manufacture
- [redacted] concerning SST failure with [redacted] assay
- [redacted] concerning OOT temperature
- [redacted] concerning OOT temperature
- [redacted] concerning the use of unauthorised polybags for material contact

[redacted] was reviewed concerning a related substance test failure following the technical transfer of the RS method to a CMO.

[redacted] a temporary change control relating to the omission of up to one stability test point during the Covid-19 was reviewed and a deficiency cited.

The latest PQR's were reviewed for [redacted] (Jan20 to Dec20) and [redacted] Oct19 to Sep20). The PQR's were reasonably comprehensive however gaps were observed and cited.

Quality review meeting minutes and associated documentation for April and May 2021 were reviewed without comment.

C5 Personnel

Personnel interacted with appeared suitably qualified and competent in their allotted roles.

The general training procedure ([redacted]) and the QC training procedure ([redacted]) were reviewed without comment. The training file for a recently appointed Senior QC Analyst [redacted] was reviewed without comment.

C6 Premises and Equipment

A formal process was in place for the receipt of goods, including a review of supplier status. Following receipt, goods were sampled according to the site sampling plan. There was no assurance that this plan was statistically valid, nor equivalent or better than an AQL methodology. Storage was orderly, though some examples were observed of goods being stored in warehouse locations without the required segregation. Temperature was monitored and controlled in the main storage areas to 15°C to 25°C, with cold storage (2°C to 8°C) and CD storage also being used where applicable. Temperatures were continuously monitored through the EMS system.

A calibration planner was in use for the site which was reviewed without comment.

C7 Documentation

The documentation system was mature and reasonably comprehensive.

A full review of a [redacted] BMR was performed and found in general compliance however, there was no process to ensure the retention in readable form of data from faint balance printouts, even though the BMR not including printouts was subjected to scanning for retention of an additional electronic copy.

C8 Production

Production was segregated into two discrete units, Licenced and Unlicenced (Specials). The units were under separate management structures.

The licenced manufacturing area was inspected, and whilst in general compliance a number of deficiencies were raised in respect to clean status labelling, calibration status labelling and general fabric of the area. The area was equipped to produce non-sterile liquids.

The unlicenced manufacturing area was inspected in brief as this was inspected at length during the previous inspection, viewing operations from accessible windows on this occasion. The process for order receipt, BMR production and batch assembly were reviewed more extensively and found to be in general compliance.

C9 Quality Control

Analytical QC, excepting GC analysis, was contained within a single laboratory. A review of HPLC data integrity was performed and weaknesses with the processes applied were identified and cited. Dissolution equipment preventative maintenance and calibration was also reviewed.

Product development had recently occupied separate laboratories on site which were not inspected.

Microbiology was separate from analytical QC and handled environmental monitoring, water sampling and TMC. EM data was reviewed prior to the site inspection and no deviations raised.

C10 Outsourced Activities

Not reviewed at this inspection

C11 Complaints and Product Recall

Two complaints were reviewed:

- [redacted] concerning an unlabelled bottle of [redacted] found in the market. This was the second similar complaint on the batch, manufactured at a CMO.
- [redacted] concerning container closure issues with [redacted] which was reported to DMRC

C12 Self Inspection

Not reviewed at this inspection

C13 Distribution and shipment (including WDA activities if relevant)

Not reviewed at this inspection

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

None

D3 Others

3.1 The management of deviations was deficient in that:

3.1.1 In respect to deviation [redacted] in respect to a site wide power outage, there was no reference in the deviation in respect to which stability study batches were impacted, nor a list of impacted HPLC analyses.

3.1.2 In respect to deviation [redacted] concerning the transcription of a batch record which had been damaged through a product spill, there was no record of a formal check on the accuracy of the transcription.

3.1.3 In respect to deviation [redacted] concerning the allocation of an unapproved material to manufacturing, there was no CAPA to address the root cause of a system failure to change the material disposition within the [redacted] software.

EU GMP C1.4(xiv), C1.8(vi), C1.8(vii)

3.2 The management of product quality reviews (PQR's) was deficient in that:

3.2.1 Reports were not uniquely referenced within the quality management system

3.2.2 With respect to the [redacted] report, there was no commentary on the forecast for impurity B, which did not appear to be scientifically justified.

EU GMP C1.10(vii), C4.3, C6.27

3.3 The management of temporary change controls was deficient in that there was no clear indication as to the restriction in time or batches that the change control would be operational, as exemplified by [redacted] concerning a temporary provision to omit a single stability study timepoint due to staff shortages during the Covid-19 pandemic.

EU GMP C1.4(xii)

3.4 The manufacturing facility was deficient in that:

3.4.1 There was no clear instruction at material receipt to prioritise cold chain and controlled drug products to ensure they are not compromised.

3.4.2 There was no scientifically justified assessment for the use of the raw material and packaging sampling regime on site.

3.4.3 Although side to side segregation was in place within the storage areas, more than one product was observed in several instances to be within a single storage location, and materials were observed to be stored in locations that were labelled for other materials.

3.4.4 There was no indication within the manufacturing area of the clean status of equipment

3.4.5 There was no indication at the point of use of the calibration status of equipment within manufacturing.

3.4.6 There was no instruction or justification in respect to changing the in-use expiry date of pH buffers once the original manufacturers container was opened.

3.4.7 Silicone sealant used within manufacturing was observed to be peeling which provided a risk of inadvertent product contamination.

EU GMP C3.9, C3.18, C3.41, C5.7, C5.13, A8.2, A8.5

3.5 Laboratory operations were deficient in that within microbiology, there was no indication to a change the in-use expiry of Gram stain reagents and [redacted] observed to be stored outside of the manufacturers stated storage conditions of 20°C to 25°C

EU GMP C6.21

3.6 The management of data integrity was deficient in that:
3.6.1 There were no audit trails of balances used within the facility
3.6.2 The time zone on computers was able to be changed without authority which altered the time
3.6.3 There was no system in place to ensure that printouts attached to batch records retained the data throughout their retention period. Several printouts were observed with very faint text and no copy in durable media was available.
3.6.4 All HPLC sequences were manually integrated which introduced analyst subjectivity and variation into the assessment
3.6.5 HPLC data was stored on local drives for 10 minutes before being copied to a backup
3.6.6 The incremental backup on HPLC data used would permit the overwriting of data should it be modified on the local machine.

EU GMP C4.10, A11.1, A11.9, A11.10, A11.17

D4 Comments

None

Section E Site Oversight Mechanism

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

Section F Summary and Evaluation

F1 Closing Meeting

Personnel identified in B3 above were present and accepted the deficiencies without dissention.

F2 Assessment of response(s) to inspection report

The response was returned within the prescribed timeline and was considered acceptable.

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
GMP as required by the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	X
The Medicines for Human Use (Clinical Trials) Regulations 2004	
Regulation 5 of the current Veterinary Medicines Regulations	
Regulation C17 of the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 06Jul2021

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	0	Last inspection:	2
Other deficiencies this inspection:	6	Last Inspection:	3

(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)

[redacted]

(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	

[redacted]

(g). GMP or GDP certificate conditioning remarks required as a result of risk-based decisions 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]

(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