Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Roche Products Ltd
6 Falcon Way, Shire Park
Welwyn Garden City, Herts AL7 1TW

Head Office:
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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/ MIA(IMP)/ WDA (H)/ 31

Licence Holder/Applicant: Licence holder

Details of Product(s)/ Clinical trials/Studies: This site is a batch release site for a number of licensed products. In addition, the site imports some unlicensed products and coordinates wholesaling activities where storage is conducted by a contractor. This site has previously coordinated clinical trials and had IMPs packed by a contract packer. No trials are currently taking place. Some licensed products are also imported after batch release at sister sites within Europe.

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	N
Importing	Y
Laboratory Testing	N
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: Import of unlicensed medicines, Wholesaling (storage at a contract site), IMP activities	Y

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

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Site Contact: [redacted]

Date(s) of Inspection: 9 May and 1 June 2017
(The start time on 9 May was delayed until mid-morning due to the inspector having an IT problem which meant an unplanned trip to Victoria. Additional time was arranged on 1 June to make up the inspection time to one day)

Lead Inspector: [redacted]

Accompanying Inspector(s): n/a

Case Folder References: GMP/GDP/IMP 31 - 86087 -0013

Section B General Introduction

B1 Background information

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The site operates as a virtual wholesaler with storage and distribution being undertaken by a contractor (Alloga).
Batch release is undertaken for some licensed products. These currently include [redacted] Laboratory results from sister Roche sites are used for release.
A larger number of products are released and QP certified by European Roche QPs. Data supplied to the inspector indicated that 35 products are in this category.
Unlicensed imports are sourced and supplied once approval is obtained from the INS unit.
This site has previously managed clinical trials. No trials are ongoing at this time but the site expects future trials to materialise.

Previous Inspection Date(s): 27 February 2013

Previous Inspectors: [redacted]

B2 Inspected Areas

Company presentation
Licence content
Action taken in response to previous inspection
Unlicensed products
Notification systems
Stock balances and tracking notifications
Identify centrally authorised versus unlicensed in UK
TSE information
Passing warnings to prescribers
Export-checking recipient country allows imports
Adverse event reporting
Checking supplier and customer bona fides
Import and assembly of investigational products
SOP listing and review
Contract packer agreements and audits
Product specification files
Reference and retention samples
Storage and distribution arrangements
Certification process
Licensed products
Starting materials and TSE checks
API compliance
Pharmaceutical quality system
- product quality reviews
- complaints
- deviations and non-conformances
- change control
- CAPAs
- training
- management meetings
- artwork controls
- data integrity

Documentation
Quality control
Outsourced activities
Complaints and product recall
Self inspection
Distribution and shipment

Wholesaling activities
Scope of activities at Welwyn
Customer and supplier bona fides
Order taking
Recalls returns and complaints
Storage environment and temperature mapping
Audits of contract storage sites
Contracts and agreements

Limitations / exclusions to inspected areas

Covering these four areas in one day inevitably means that inspection is at a high-level.

API registration activities were not included in this inspection.

B3 Key Personnel met/contacted during the inspection

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[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	2 May 2017	Y
Compliance Report	2 May 2017	Y
Comments:		

Section C Inspector's Findings

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C1 Summary of significant changes

Several IT changes have taken place. These include a new artwork management system [redacted], the use of [redacted] for lot tracing, and a system for storage of regulatory documentation (GPRS).
API registration for [redacted] has been undertaken.
There has been a reduction of paper-based systems for QMS processing. This includes the implementation of [redacted] discrepancy management module (2014) and additional modules for action tracking and change management (2015)

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

None

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

None

C2 Action taken since the last inspection

The previous inspection deficiencies were all classified as "other". An acceptable written response was received by the previous inspector.

C3 Starting Materials

General

For licensed products checks and evaluation are carried out by Corporate staff.

Compliance with TSE Guidelines

TSE checks on APIs and excipients are mainly the responsibility of the sister sites in Switzerland. One problem was noted with the age of the TSE certificate for an unlicensed medicine-see below. One further deficiency was reported related to this area as the company do not have any formal stated requirements for the content and renewal period of TSE information.

API Compliance

The compliance and auditing of API suppliers is not the responsibility of any staff at Welwyn. This activity is carried out by staff at the Swiss sites.

C4 Pharmaceutical Quality System

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Product quality reviews are the subject of an SOP which also encompasses quality risk management. The latest product quality review for [redacted] tablets covered the period for calendar year 2015. This document was not formally approved until 7 September 2016, Local procedures allow a period of up to 8 months to formally approve PQR documents.

A review of the company's deviation system resulted in the selection of some incidents for wider review. Deviation [redacted] dated 4 February 2017 concerned a failure to complete to product quality reviews with inappropriate timelines. The reason given for this issue was "inadequate tracking of schedule".

The issue of overdue PQRs was explored further. It was established that a number of PQR documents had not been completed within acceptable timelines e.g. [redacted] (PQ are period 1/4/15 231/3/16) had not been signed off until 4 May 2017. A similar issue was noted with a PQR for [redacted] (1/3/15 to 29/2/16) which had not been signed off until 7 March 2017. When the issue was looked at further it was noted that they have been a larger problem which the company now seem to be resolving.

The system for management quality meetings was discussed but the company. There is a monthly meeting which contains a review of relevant KPIs. The scope content and frequency of the meetings appeared to be acceptable.

There is a formal system for approval and tracking change controls within the company. Just two change controls had been progressed into 2017 by the time of the inspection. Approval and documentation were reviewed and found to be acceptable. One example seen involved transfer of temperature monitoring data to a new server which had been implemented at the end of January 2017. Tests for the completeness and accuracy of the data had been carried out together with additional security checks.

The company have ready access to any corporate audit reports. The contract manufacturer for [redacted] tablets is [redacted] France. The latest audit report was requested and had been carried out on 4th and 5 July 2016. This contractor is also a manufacturer of sterile products and the latest audit had focused mainly upon sterility test and OOS issues with little content on non-sterile manufacture.

C5 Personnel

Training records for one member of staff were selected and reviewed. This included both induction training and recent ongoing GMP training. There were no adverse findings for this area.

C6 Premises and Equipment

No manufacturing activities take place on this site and there is no product storage.

C7 Documentation

The technical agreement with [redacted] was requested and reviewed. It was noted that the document was dated 13 June 2014. Some shortcomings were noted in the document. It was noted that there is no requirement to repeat temperature mapping of the storage areas at regular intervals. Another concern with this document was the fact that there appeared to be a number of errors present between sections 9.6.3.4 and 9.6.3.9. These appear to have errors for the role of the contract acceptor and some fields had no responsibility attributed to either the contract giver or the contract acceptor.
[redacted] can also be involved in export packaging. There was no information include included about requirements for export packing and specifically the use of data loggers. Product can be shipped to Malta by [redacted] The inspector was informed that data loggers are routinely included in such shipments.

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The technical agreement with the contract QP [redacted] was also reviewed. This document had no stated review or validity period.

SOP [redacted] covers the provision and content of technical and quality agreements. There was inadequate coverage of QP agreements with the only mention of technical agreements referring to new IMP site studies.

C8 Production

No production takes place at this site.

For investigational medicinal products, the main contractor is [redacted] A master quality agreement is in place with [redacted] covering package, storage and distribution of investigational products.

Procedures for the approval of bulk drug product, packing operations and batch disposition of investigational products were reviewed briefly, no deficiencies were reported for these areas.

C9 Quality Control

Paperwork systems for the release of licenced products were reviewed. The requirements and documentation were considered to be satisfactory.

C10 Outsourced Activities

An audit of the [redacted] operations had taken place on 8 and 9 November 2016. This had been led by local QA Specialist [redacted] who was accompanied by backup QP [redacted] The audit report was issued on 5 December 2016. The report contained six minor observations and three recommendations. Response and closeout confirmation was subsequently requested and considered to be acceptable.

C11 Complaints and Product Recall

The Complaints SOP covers the investigation, reporting and distribution of product customer complaints. The document seen was version 4 which was effective from February 2017. Suitable follow-up measures were included if information/samples were not provided. A tracking log is in place to ensure appropriate timescales and closure.

A number of complaint reports were requested for further consideration. Some discussion took place about complaints related to [redacted] There had been a number of visual defects concerning potential crimping defects. Replenishment orders had been blocked but some supply had been allowed to prevent an out of stock situation at the patient level. Examples included [redacted] where a defective metal crimp noted during a spraying-in operation. Other examples included [redacted] A summary report for this problem was reviewed and considered to be acceptable. DMRC communications were also seen for this area.

The product recall SOP was reviewed. An SOP update had taken place in January 2017. A suitable contact list was provided and contact details appeared to be current and correct.

Suitable procedures are in place for conducting mock recalls in the absence of a conventional recall. The report from the latest mock recall, conducted in October 2016, was requested and reviewed. Stock information was obtained from [redacted] in a timely manner.

C12 Self Inspection

This area was not covered and should be included in the next inspection.

C13 Distribution and shipment (including WDA activities if relevant)

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[redacted] are responsible for storage, picking and distribution activities for customers in the UK and Malta. Products are distributed in temperature controlled vehicles and by the use of passive shippers.

Customer bona fides checking and stock procurement are the responsibility of [redacted]. Orders and data are transmitted electronically between [redacted] Complaints are handled at Welwyn Garden City. Recalls are initiated by [redacted] but would then be effected by [redacted]

Customer bonafides are covered in a dedicated SOP which was seen by the inspector. The scope of this also includes the opening of new accounts. The registration of pharmacy customers is checked on the GPC website. There is a separate SOP for checking for revoked customer authorisations. This is checked on a monthly basis. If authorisations have been revoked, then the customer is blocked in SAP. In addition, accounts which has not been used for three months would be routinely blocked.

The SOP for reading and downloading datalogger information was also reviewed and considered to be acceptable.

C14 Unlicensed medicines

The inspector reviewed recent activity on Documentum prior to the inspection. This revealed that the site is active but has a comparatively low number of notifications. The main purpose of such medicines is for post-trial use or compassionate supply to patients.

Documentation for unlicensed medicines imports was reviewed. One product received from Genentech, South San Fransico, was reviewed. The documentation been checked by the QP. It was noted that the TSE certificate was dated January 11, 2012. The inspector considered that a newer certificate should have been requested and received in this case.

An appropriate tracking system is in place for the receipt and use of notifications.

The system for handling and approving requests for unlicensed medicines was reviewed together with systems for reporting adverse events.

It was noted that there was no formal mechanism to pass on any warnings or advice from [redacted] to the prescriber. There is currently no export of any unlicensed medicines. The inspector commented that checks should be made that local Regulators permit the import of unlicensed medicines before any export commences.

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

None

C15 Annexes attached

Annex 1 site risk rating
Annex 2 list of deficiencies

Section D List of Deficiencies

See Annex 2

Section E Site Oversight Mechanism

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

Section F Summary and Evaluation

F1 Closing Meeting

A routine closing meeting was held with the company. A positive response was given to all the deficiencies which had been presented stop

F2 Assessment of response(s) to inspection report

A response was received on 30 June 2017. The response was considered generally acceptable. Target due dates, in the response, range up to 30 September 2017. The inspector has decided to finalise this report and issue a GMP and GDP certificate on the basis of this response.

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 GMP and GDP:

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.

Name and Dated Signature of Inspector (s):

Signed: [redacted] **Dated:** 11 August 2017
Name

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	0	Last inspection:	0
Other deficiencies this inspection:	4	Last Inspection:	5

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

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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

The last inspection was two inspector-days. Consideration should be given to allowing more than one inspector-day for the next inspection.

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(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	

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

Expert / Operations Manager / CMT (delete as appropriate)
Risk Rating:
Comments:

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[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.gsi.gov.uk

Annex 2
Inspection of:
Roche Products Ltd
6 Falcon Way, Shire Park
Welwyn Garden City, Herts AL7 1TW

Inspection Date: 9 May and 1 June 2017 (total time one day on site)

Ref: Insp GMP/GDP/IMP 31/86087

FAILURES TO COMPLY WITH THE EU GUIDE TO GMP

1. Critical
None

2. Major
None

3. Other

3.1 **Technical agreement concerns**
3.1 1The technical agreement with Alloga needs improvement:-
3.1.1.1 the document did not include the requirement to repeat temperature mapping of storage areas at regular intervals
3.1.1.2 Section 9.6.3.4 to 9.6.3.9 appeared to have errors for the role of the contract acceptor and some fields with no responsibility attributed to the contract giver all the contract acceptor.
3.1.1.3 No information was included about export packing and use of dataloggers for such shipments.
3.1.2 1 The TA with contract QP (BJ) had no stated review or validity period.
3.1.2.2 SOP 001519 on technical and quality agreements did not cover QP agreements with the only mention of technical agreements referring to new IMP site studies
Ref EU GMP Guide: 4.5 & 7.14

3.2 **Unlicensed medicines**
Systems for processing unlicensed medicines do not cover the situation where the MHRA requires additional information to be provided to the prescriber.
Ref Schedule 4 Human Medicines Regulations 2012

3.3 **TSE certification**
3.3.1 The company do not have formal stated requirements for the content and renewal of TSE information.
3.3.2 One certificate seen was dated Jan 11 2012. A maximum of three years life is the normal expectation for this documentation.
Ref EU GMP Guide:1.4(vi)

3.4 **Product quality reviews**
A number of PQR documents have not been completed within acceptable timelines eg Rocaltrol soft caps (1/4/15 to 31/3/16) signed off on 4 May 2017 and Konakion (1/3/15 to 29/2/16) signed off on 7 March 2017. [It was noted that there had been a wider problem of delayed PQRs with a number of other PQRs approved earlier in 2017 outside the normal timelines]
Ref EU GMP Guide:1.10

(Comment follows on next page)

Comment

Although there is currently no export of unlicensed medicines the company should be aware that checks should be made that local Regulators permit the import of unlicensed medicines before any export commences.

<END>