INSPECTION REPORT

AstraZeneca
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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection and Site hand over

Licence or Reference Number: Manufacturer's Licence No. MIA, MS 17901
Manufacturer's Licence No. MIA(IMP) 17901
Wholesale Dealer's Licence No. WDA(H) 17901

Licence Holder/Applicant: AstraZeneca

Details of Product(s)/ Clinical trials/Studies: Multiple (See Imports, Appendix 1)

Activities carried out by company:	Y/N
Manufacture of Active Ingredients	Y
Manufacture of Finished Medicinal Products – Non sterile	Y
Manufacture of Finished Medicinal Products - Sterile	Y
Manufacture of Finished Medicinal Products - Biologicals	Y
Manufacture of Intermediate or Bulk	Y
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	Y
Other: WDA(H)	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 15th to 19th Jun 2015
Lead Inspector:
Accompanying Inspector(s [redacted]

Final Conclusion/Recommendation:
The site operates to a satisfactory level of GMP & GDP. A type 1 letter has been sent and a satisfactory response received. Continued support of the licence will be recommended to the Licensing Authority. Please refer to Annex 1 for re-inspection frequency.

Name and Dated Signature of Lead Inspector:

Signed: [redacted] **Dated:** 26th Aug 2015
Rachel S. Carmichael

Section B General Introduction

B1 Background information

The Astrazeneca, Macclesfield site covers approximately 100 acres. This is a large and complex operation and is inspected on a rotational program. The site and the associated inspection programme can be split into subparts.

1. Tablet manufacturing and the warehouse
2. Packaging operation.
3. Sterile area.

This visit was the inspection of the Tablet manufacturing and the warehouse as well as a hand over inspection of the Site to Mr Alan Moon who will the main Inspector for this site going forwards. Aspects of the quality system were reviewed in some detail, and the tabletting operations were inspected in full. The on-site Chemistry laboratory operations were not inspected (Having been inspected with Stability in 2014) but the microbiology laboratory was.

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Discussions were held concerning the API activities for [redacted] At the time of the Nov 2013 inspection an API campaign was ongoing with the anticipation that production would end in Q1 2014. A valid API GMP certificate was in place. Having stopped the process it was found that more batches were required. Advice was given concerning requesting an API inspection from [redacted] (the site is registered as an API production site but needs a GMP certificate for some markets).

The site maintains a specials license for the importation of unlicensed medicines on a named patient basis. This could be used by either the commercial operations or the pharmaceutical development division. The pharmaceutical development division separately hold an IMP license. The production elements of that licence have ended on site but the commercial division, will maintain the IMP license in the event that comparators may be required.

The site also holds a wholesale dealing licence, which was inspected on this occasion with a focus on material supplied for manufacturing.

The strategic plan for Macclesfield continue to progress. The site will continue with [redacted] and [redacted] and become a key importer/tester of product made outside of the EU for packaging. The manufacture of some non sterile solid dose forms will also continue and the site is a major centre for stability testing.

Previous Inspection Date(s): 9th to 12th Jun 2014

Previous Inspectors: [redacted]

B2 Inspected Areas

See Annex 2

Limitations / exclusions to inspected areas

None

B3 Key Personnel met/contacted during the inspection

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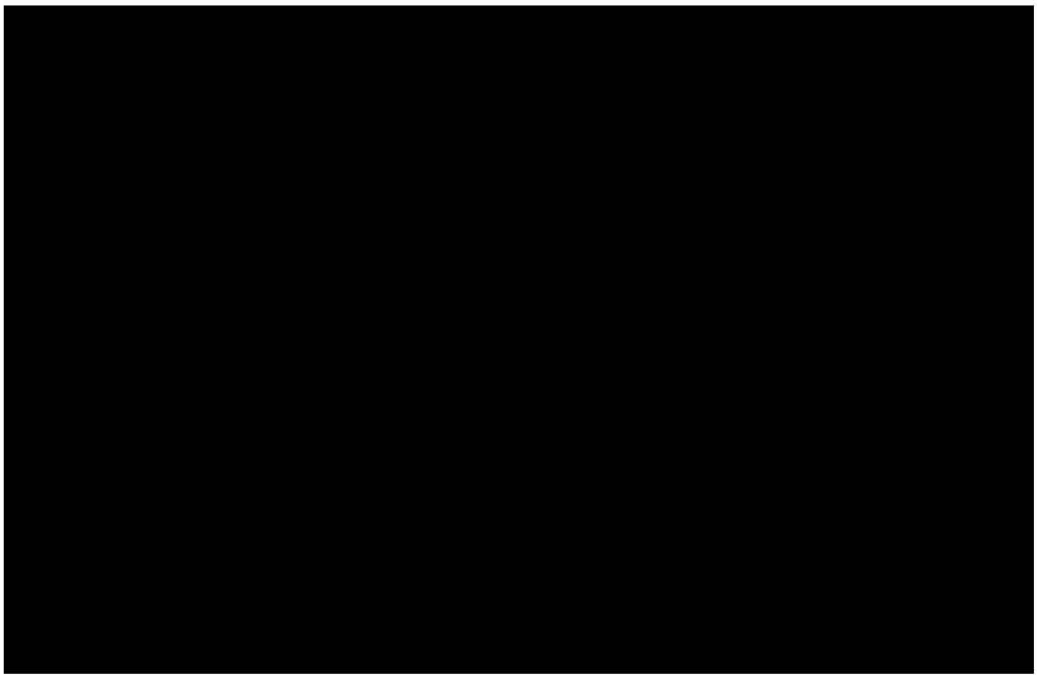

B4 Documents submitted prior to the inspection

The compliance report and the Site master file.
At the last inspection it was noted that the Site Master File lacked clear drawings of the full site layout. This has now been addressed and is a marked improvement in terms of clarity.

Section C Inspector's Findings

C1 Summary of significant changes
Detailed changes are recorded in the compliance reports held in the case folder.

Changes since Previous Inspection

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There have been a lot of changes at this large site including personnel and equipment

Future Planned Changes

The site has a number of planned changes. Key elements discussed during the week were:

- SPP5 building and go live of new [redacted] production are
- Re-introduction of API activities
- Longer term plans to relocate the packaging lines and distribution warehouse. This project had plans through to 2020 for completion.

C2 Action taken since the last inspection

At the last inspection issues were identified with regards computer system management. A Computer Systems Key Performance Indicator has been introduced. The KPIs since July / September 2014 show that there are still issues with de-registration of computer systems and identifying system owners and controllers. The aim to have a plan by 30.9.15, de-registration (to ensure system retirements in a managed way) will take around 2 years. "Critical" systems have been identified and their review process has commenced.

C3 Starting Materials

General

An SAP system is in use and controlled on a global level.

The list of materials that have an automatic usage decision assigned as part of their Material Master was reviewed as a sample challenge of the system set up. There were no obviously inappropriate materials in the listing.

Compliance with TSE Guidelines

TSE control systems are in place but were not inspected in detail at this inspection.

API Compliance

Detailed systems are in place at a global level and were not inspected in detail on this occasion. The requirements are managed through the Global External Supply (GES) group which is not based in Macclesfield. Some aspects were reviewed (see section C8, production).

C4 Pharmaceutical Quality System

The site operates a sound and proportionate quality system. The procedures system appears to be generally in control, staff are trained and overall the level of execution showed compliance to the procedures. New requirements are reviewed and addressed in line with the procedure, Management of changes to external regulations within operations. Large changes such as the current updates to Chapters 3 and 5 result in a centralised response to ensure resources to identify an appropriate process.
There are defined Site Quality Metrics in place and a procedure to control the procedure (SOP 203340). The reporting of quality and compliance performance to management.
Product Quality Reviews (PQRs) are generally completed in the first three months of the year and as a result primary sign offs can be late. The product from imports are reviewed as part of the packaging PQRs.
The deviations system and a selection of deviations were reviewed
Form [redacted] is the Root Cause tool. No issues were identified.
[redacted] related to a confirmed laboratory failure out of specification. The investigation was detailed but lacked a minimum format for parts of the paperwork – for example the Manufacturing investigation required structure – a title, names – people involved, job titles of Approvers, basic sections such as Batch record review.
Some deviations (such as [redacted] are not clear as to how the boundary of the "event" has been defined.
"Events" of low risk are recorded and can be tracked and trended – the tracking and trending is recorded in the area quality council database. The tablet quality council summary was detailed.
Incident [redacted] was a quality note (an event identified as low risk). The event related to using the purified water system prior to qualification completion. The classification of the event as low

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risk was not appropriate and the actions taken to prevent re-occurrence were inadequate. The Staff failed to recognise that only qualified systems and equipment may be used even though this was set out in the qualification pack.
SOP [redacted] is the procedure to Raise and progress a change in UK Operations (Macclesfield). Control mechanisms are in place either paper based or electronic depending on the system. A selection of changes were reviewed including the upgrade of the [redacted] production facility, a change relating to a server update and a change relating to the integration of the diabetes portfolio (from BMS). [redacted] is a peptide product with a 52 day release test. The importation for packing and QP Certification had been introduced to site but with inadequate training records for the affected Staff in that the training was not formal and documented. There was no record of a QP Site visit report

C5 Personnel

Personnel met during the inspection were knowledgeable and able to describe their roles confidently.

Appropriate systems are in place for training including periodic GMP / GDP training and competency assessments.

C6 Premises and Equipment

The change control, calibration, validation and cleaning systems were in place and reviewed. The company had made progress with the implementation of the revised EU GMP Chapters 3 and 5 in relation to use of the toxicological tool for calculation of permitted daily exposure limits. The company stated that it expected to be fully compliant with the requirements for existing products by the date of these coming into effect in December 2015. There are outstanding queries concerning the "clean" hold time of active materials dispensing in the [redacted] facility which were raised in the post inspection letter.

An overview of the refurbishment project for the Special Tablets Facility, STF (where [redacted] is made) was presented. This had been initiated in April 2014 under change control [redacted], with the VMP issued in Jun 2014. The facility shutdown for the first phase of refurbishment which included upgrades to the utilities and fabric of the facility commenced in August 2014 – this had been completed and handed back to manufacturing for GMP use prior to the inspection. The VMP summary report was being routed for final approval at the time of inspection however it was demonstrated that a formal GMP approval had been performed prior to restarting manufacturing activities. The second phase of the upgrade was planned for 2016 and will include upgrades to process control systems and also some areas of the facility fabric that were not fully completed during the first phase due to time constraints to avoid interruption of supply to the market.
Note: The Inspector incorrectly referred to this part of the site as SPX on multiple occasions.

An overview of another project to redesign the packaging and distribution warehouse areas with a plan to 2020 was discussed at a high level. A currently disused highbay warehouse will be refurbished and expanded initially as an automated warehouse facility. The existing distribution activities will then be relocated before the existing warehouse area will be refurbished for the existing packaging areas to be relocated into. A discussion was entered into regarding the concept of using automated systems to potentially control rejected materials. This would need to satisfy the requirements of EU GMP Chapter 3 (3.23) and be appropriately risk assessed and justified.

The company introduced mapping of controlled cold areas within the past 12 months and the requirement for annual re-mapping has been established. The receiving area of the warehouse had not been mapped and is only monitored at a single point. Appropriate procedures and systems are in place for both Security and Pest Control.

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SOP [redacted] was the instrument calibration procedure for the weigh feeders in [redacted] production. The operational range is verified. The facility uses compressed air but lacks the normal standard checks including microbiology as part of the 12 month check. The company had identified this for themselves and are implementing point of use testing by mid September.

C7 Documentation

Documentation reviewed was generally clear and logically designed.

The site operates a deviations system which is predominantly paper based and then the records are entered by deviations managers into an electronic system called ICON which is where the decisions are recorded. The site lacks a documented description of how to manage such "hybrid" systems. [redacted] is the Data and Documentation Policy. [redacted] is the Standard for the use of electronic records and electronic signatures (a global IT Standard).

C8 Production

The full warehouse was inspected from Incoming materials to despatch. Any issues were raised in the deficiency letter. The facility is of a certain age and despite a strong maintenance programme there are some issues within the structure of the building (relating to the drains), wood within some cold rooms and lack of seal to a door but given the scale of the facility overall it was acceptable and well managed. There were issues with dress control on entry into the warehouse – there was a lack of adherence for the step over rules for entry into the facility by Staff that were in the lobby. The sampling areas for APIs, excipients and packaging components were inspected along with the room where testing of packaging components occur. NIR testing is carried out for identity testing in materials receipt – the data integrity requirements were discussed and appeared satisfactory. Some aspects of the control of storage rooms and access to obsolete changing areas was poor and the issues were raised in the deficiencies.

The tablet production areas were inspected in some detail. These areas are within the Pharmaceutical Production Building and comprise:

- Special Tablet Facility (STF)
- Tablet Processing Facility (TPF) and TPF Dispensary
- Tablet Expansion Facility (TXF)
- Tablet production area 2 (TPA2)
- Tablet Coating Facility (TCF)
- Tablet Inspection Facility (TIF)
- Capsule Manufacturing Facility (CMF) – to be decommissioned.

[redacted] is manufactured in STF and had been subject to a recent refurbishment. A second stage refurbishment is planned. The processing steps in this area were not fully recorded and possibly as a result of the facility being a dedicated plant the EU GMP required labelling standards were not met for in process equipment. A Major deficiency was raised and a detailed review of the critical settings was conducted through the review of the batch record. The process had an electronic print out at some stage in the past but due to the systems age it had been withdrawn. At that time it appears that the batch records may not have been appropriately updated to capture the processing information that ought to have been there (and may have been in the historic computerised system). The process is quite unique with an extrusion and microwave drying which was novel when designed in the 1980s.

In some of the tabletting areas and in some void area there was an inconsistent standard applied for the storage of equipment (including labelling) and the standards of housekeeping

applied (raised in the PIL). Some areas were not appropriate. The Site lacks a consistent procedure and labelling standard (or form template) for equipment that is out of use.

A brief inspection of the main Packaging hall was conducted – the area had been refurbished and line to line segregation improved since the last inspection. While the changes appeared to be predominantly superficial it has a marked improvement on the perception of the space as a GMP area. At the last detailed inspection of Packaging some of the aligned but peripheral areas had poor levels of housekeeping – these were sampled at stages throughout the week and demonstrated significantly improved levels of control. "Owners" have been assigned for ensuring areas are clean and tidy and this change appears to have worked and brought true improvement at the time of the inspection. A capsule product has been introduced for packing on site [redacted] The introduction and controls were reviewed – the packing here is for the EU and the rest of world into a [redacted] bottle containing [redacted] with a child resistant closure. The primary packing takes place into unlabelled containers placed in labelled boxes which are then labelled and hand packed into market specific shippers. There are currently no other bottle packed products on site. The GMP Certificate and the agreement with the manufacturing site were reviewed – the agreement is managed through the [redacted] group. The management of [redacted] from a temperature and humidity perspective were reviewed and no significant issues identified.

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C9 Quality Control

Microbiology QC. The Microbiology QC laboratory function was split into three teams namely:

- Product Testing ([redacted] of raw materials and finished product)
- Process Assurance (environmental monitoring, media fills and control of biological indicators)
- Water Testing and Support (water analysis, media preparation, sterilisation of equipment and identification of organisms)

The main laboratory in the QA building consisted of a number of separate suites either side of a central corridor and overall appearance was clean, tidy and orderly.

Environmental monitoring of non-sterile manufacturing areas was performed by Microbiology staff in accordance with a defined schedule. For aseptic areas, the routine monitoring is performed by Production staff (trained by [redacted] with monthly monitoring performed by [redacted] staff in addition to this. There were satellite laboratories within each of the aseptic manufacturing buildings where environmental monitoring plates were incubated and read to minimise the risk of external contamination during transfer to the main laboratory. Any contaminated monitoring plates were transferred to the main laboratory for further identification. Monitoring was performed using TSA with a single incubation temperature of 30-35ºC. The company had performed a study to support this approach.

There were several walk-in incubators available in the main laboratory and these were routinely temperature mapped on a four-year rolling cycle. Separate reach-in refrigerators were in use for cultures and samples respectively.

All agar plates used for routine testing were purchased ready to use and were received on a weekly delivery. A sample of the media from every delivery was tested for growth promotion and a sample from every batch of media received was also tested. Quanti-cult standard organisms were used. These were accepted from the supplier on the basis of the certificate of identification and were also used for the positive controls on the identification equipment [redacted]

Fluid media was generally prepared and sterilised in-house from supplied dehydrated media and purified water. Two double-ended [redacted] autoclaves were available which were revalidated on an annual basis, with a selection of loading patterns performed each year. Validation of these autoclaves was not reviewed at this inspection however it was noted that the

procedure referred to a sterilisation exposure time of 22-32 minutes at 121ºC which was longer than the manufacturer's recommended 15 minute exposure period. The electronic lab notebook system was used to prepare the batches of in-house media and to record all growth promotion results.

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The level of identification of isolates from environmental monitoring was dependent upon the location of the sample – all isolates from manufacturing areas were [redacted], with full species identification performed for any isolates from grade A zones or from personnel monitoring and any [redacted] isolates.

The sterility testing suite housed four half-suit isolators within two large segregates rooms which required a gown change to access. Three of the isolators were hard-sided, with one soft-walled unit and all were sanitised by VHP with defined load configurations which allowed for six batches of [redacted] product to be tested per session. The most recent requalification of the VHP sanitisation was reviewed [redacted], Apr 2015) and found to be generally acceptable. The routine loading pattern was based on the validation however a diagram rather than photograph was used therefore this could be made clearer. The isolators were tested for filter integrity and classification on a six monthly basis and routine monitoring was performed during each test session. Due to the nature of the [redacted] product, a sterility test method had been developed which included homogenisation of the depot in sterile saline prior to inoculation into the sterility test media. Each product syringe was also rinsed with sterile test media which was then incubated (10 with [redacted] and 10 with [redacted] . The method was also validated using [redacted] per inoculum for growth promotion and not [redacted] to further challenge the sensitivity of detection due to product settling from the homogenisation process. As [redacted] is an established product, the sterility test method validation had been updated since initial validation in 1994 in line with Pharmacopoeial changes. The most recent work associated with this ([redacted] – May 2012) was reviewed and no issues were noted.

Four LAF benches were available within the water testing laboratory and vacuum manifolds and testing equipment were sterilised on a daily basis in an autoclave. The adjacent room housed a further four LAF benches which were used for non-sterile product testing. Specifications for testing were printed directly from the LIMS each time of use.

The Microbiology group was also responsible for management of Biological Indicators and performed enumeration and identification for purity on each lot received. There were requested by Sterilisation Officers for use in sterilisation validation activities before being returned to [redacted] for incubation and assessment.

Endotoxin testing was performed for products ([redacted] plus other imported products and stability testing) and water. Chromogenic methods were primarily used however gel clot was also a registered method for [redacted] as a backup. The validation of the endotoxin testing for [redacted] was reviewed [redacted] and no issues were noted.

All staff within the [redacted] department were subject to annual sight checks and were required to pass a challenge test for reading media fills.

C10 Outsourced Activities

No aspects of outsourcing were inspected in detail on this occasion. The process for artwork development and management was discussed – the design work was outsourced and implementation is largely managed outside the UK within the AZ organisation.

C11 Complaints and Product Recall

A [redacted] based system was in use for complaints (Global Complaints Management – GCM) and this allowed visibility across all AZ sites. Complaints may be received directly or through AZ

marketing companies and all were logged as a record within the GCM system. AZ complaints process owners performed a daily review within the system and an initial assessment was done within 2-4 days of the complaint being raised. If a complaint was deemed to be critical (patient risk) then the complaint investigation was also raised within the deviation system. For other classifications, the investigation was documented using the deviation forms but was only logged in the complaint system.

Several complaint investigations were selected for review and found to be generally comprehensive based on the available information, however it was not clear from the reports how the severity of these had been rated within the company's system. In addition, an example was seen where the investigation had been limited due to no sample or photograph being received despite the nature of the complaint including queries that related to the authenticity of the product and described changes in the packaging and labelling. There was also no formal requirement to assess the possibility of a complaint being related to falsification.

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The corporate standard for Complaints, Quality Defects and Recalls [redacted] had been updated in relation to the changes in the revised EU GMP chapter 8, however the local procedure was still under review at the time of inspection.

A mock recall had been conducted in April 2015 and was appropriately documented. The scenario used involved an 'issue' that would result in multiple batches of product being affected in order to ensure effective reconciliation could be achieved.

C12 Self Inspection

This aspect was not inspected in detail on this occasion.

C13 Distribution and shipment

This aspect was not inspected in detail on this occasion.

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

1 CRITICAL

None

2 MAJOR

2.1 Equipment and facility management.

2.1.1 The company approach towards equipment and facility status labelling is inconsistent and as a result it is not always clear as to the current status of a facility or the equipment within. Issues identified include but may not be limited to the following:

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2.1.1.1 The ex solvent coating room in TCF [redacted] was unclean. Although decommissioned this room was being used for equipment storage some of which appeared to be currently available for use within the remainder of TCF. Some of the equipment was status labelled but not all. The room is not currently a suitable location for equipment storage due to a lack of cleanliness notably the drain and adjacent area.

2.1.1.2 The Bin blending void facility within [redacted] is currently used for some equipment storage. Equipment was present without status labelling and an out of use local extract arm was stored non status labelled and unclean on the floor.

2.1.1.3 There was no status identifier on packing room G17 in TPA.

2.1.1.4 The Changing rooms and toilets adjacent to the sampling areas within the warehouse are understood to have been taken out of use. . The Ladies facility was labelled as out of use but the Gentlemans' had no label at the entrance. There was evidence to suggest that both of these areas remain in use.

2.1.2 Quality note [redacted] related to a quality note where an unqualified purified water system was used for the cleaning of a granulation suite. The response to this incident is deficient in that:

2.1.2.1 The incident has been raised at a level where no investigation, root cause analysis or remedial actions are required.

2.1.2.2 The record gave no justification for the use of an unqualified system or for ignoring controls that should have been in place to ensure that this did not occur.

2.1.2.3 The Change control for the change to the water system was clear that the system should not be used prior to the completion of Operational Qualification. The completion of such an activity is the final approval but this requirement was not met.

2.1.2.4 A section written by a second person indicated that a raw data review of the Operational Qualification had taken place prior to the use of the unqualified system but no documented proof was available with the Quality Note to support this statement.

2.1.3 Temperature controlled storage areas were deficient in the following respects:

2.1.3.1 No temperature mapping had been conducted within the Receipts Bay / holding area for goods receipt to justify the single routine monitoring point.

2.1.3.2 Wooden dividers and shelf bases were present in cold rooms used for storage of copolymer raw materials.

2.1.4 [redacted] – the coving was away from the wall at the rear of the room.

2.1.5 Dry mill [redacted] has a painted motor for the rotary valve which shows evidence of flaking. The motor is located adjacent to / immediately above the product drop through.

2.1.6 Fixed water and transfer pipes within production are not consistently labelled - with contents and, where applicable, the direction of flow.

2.1.7 Door 66 in the warehouse has an incomplete seal.

2.1.8 An open drain and channel were present within the goods receiving warehouse area.

Reference: EU GMP: Annex 15:22, 1.4(xiv), 1.8(v) 3.1, 3.3, 3.2, 3.39, 3.42, 3.4, 3.11

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2.2 Operational management is deficient in the following respects:

2.2.1 The processing steps for the pre-mix for [redacted] are not appropriately recorded.

2.2.1.1 The pre mix processing step is not recorded. There are no start times, end times. The process is to press a button and for it to proceed unmonitored. There is no print out of the processing step or alarms review to confirm a lack of issues during the processing step. The pre-mix collette [redacted] is not calibrated or periodically verified for the duration of blending.

2.2.1.2 The post drying blending stage is not recorded as it is done – no start time, no end time. The process is to press a button and for it to proceed unmonitored. There is no print out of the processing step – no alarms to show that the time requirement may not have been met.

2.2.1.3 The [redacted] that is used to take the granule from granulation to compression is weighed on the granulation floor – the weight is not second person verified and there is no print out. The weight is recorded on the batch record and on a wipeable sheet which is transferred to the downstairs compression operation while the [redacted] is on the feeding station above. The weight is transcribed into the compression batch record. There is no second person verification of the transcribed weight.

2.2.2 Operations within [redacted] *production STF* were weak in the following aspects:

2.2.2.1 The Operators cannot tell if the required weekly checks (for example on balances) have been carried out when at point of use.

2.2.2.2 The containers that the premix is held in are not identified in line with EU GMP 5.12 merely a label saying "pre mix"

2.2.2.3 The bubble point on the pre mix bench balance was out.

2.2.2.4 Procedures were not accessible within the manufacturing areas.

2.2.2.5 Water samples from the binding solution preparation vessel were not representative of the user point.

2.2.2.6 The dispensing isolator is left dusty on a batch to batch basis. The re-usable, dedicated scoop can be left for up to 12 weeks. There is no justification available for this approach.

2.2.2.7 Batch record [redacted] included a File Note which issued alternative instructions based on OCM [redacted] The original instructions in the batch record had not been amended and marked through by an Issuing Officer prior to the record being made available to operations. The instructions to operators therefore became ambiguous.

2.2.3 The step over process on entry to the warehouse is not adhered to.

2.2.4 The small storage room in sampling was overly full with materials stored on the floor.

2.2.5 Uncontrolled instructions were located in a sampling booth which included instructions required to be added to SOP [redacted].

2.2.6 The product contact plastic bag used is recorded for the coated tablets but not for other stages where it is the primary contact such as the compressed uncoated tablets (cores).

Note: *The Pantone book in packaging QC lacks a system to identify date of receipt and no replacement date is defined although the supplier indicates that the system is subject to fading and recommends annual replacement.*

Reference: EU GMP: 4.20(b), (c), 4.18(c) 5.12, 4.18(d), 1.8 (iv) 4.25, 5.20, 4.3 1.8(v), 3.8, 4.2, 5.10

3 OTHERS

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3.1 Complaints (& recall):

3.1.1 The complaints SOP [redacted] did not require investigations to include special attention to establishing whether a complaint or suspected quality defect related to falsification. (8.6)

3.1.2 It was not clear from the investigation reports how complaints had been rated within the company's system. For example complaint [redacted] related to a possible product mix up but had not been assigned as a level 1 complaint.

3.1.3 Complaint [redacted] related to questioning the authenticity of a product however as no sample or photograph had been received there was no further investigation despite the complaint description including queries relating to changes in packaging and labelling.

It is noted that the company had not notified the DMRC regarding a recall of product from Spain. (It is acknowledged that the inspectorate had been notified via an interim compliance report).

Reference: EU GMP: 8.6, 8.10, 8.5

3.2 There are no instructions as to how to handle hybrid record systems (ie where the system requires both hard copy and electronic system usage).
For example:
The Deviations management process is managed through a combination of handwritten records and word based reports that are then scanned and added to an electronic system. Currently word based typed reports in this (or the Complaints system) lack a basic (minimum) format – to include criteria such as Title, Author (name and job title), date issued and the hard copy word documents can currently lack evidence of contemporaneous approval ie. signatures and date (each page at least initialled) prior to scanning with final approval to include the job title of the approver.

Reference: EU GMP: Annex 4.1

3.3 The introduction of a new sterile product to site required the creation of a training pack for the Staff required to Certify the product. No formal training pack was raised, added to the required training curricula and as a result there was no formal record of training taking place.

Reference: EU GMP: 2.10, 2.11

4 COMMENTS

4.1 Discussions were held during the inspections concerning an ongoing investigation [redacted]
Please supply full details once this is complete.

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4.2 The QP Certification process currently has an out of date statement of compliance in [redacted] The procedure in support of the activity does not describe the statement of compliance in line with current expectations which are to reflect the spirit of the Internationally harmonised requirements for batch certification published by EMA in June 2011: [redacted]

14 Certification statement.

This statement should cover the fabrication/manufacturing, including packaging/labelling and quality control. The following text should be used:

"I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging/labelling and quality control at the above mentioned site(s) in full compliance with the GMP requirements of the local Regulatory Authority and with the specifications in the Marketing Authorisation of the importing country or product specification file for Investigational Medicinal Products. The batch processing, packaging and analysis records were reviewed and found to be in compliance with GMP".

4.3 Licence compliance

In addition to the Licence updates for personnel please include the addition of the requirements for site of physical importation of both finished product and intermediates.

4.4 The review of a batch record of [redacted] IR identified an actual weight gain reported as [redacted] (final tablet weight [redacted] with no limits applied for the final target weight of the tablets). The available Licence information indicated that the nominal coated tablet weight should be [redacted]. A Note states that the target coating weight gain may be varied from [redacted] to [redacted] so an acceptable final coated tablet weight range should be [redacted]. A further note states "based on equipment efficiency at the commercial scale, the amount of coating material transferred to the tablet surface is approximately 80% of the charged quantity." Please review the current registered information for the [redacted] tablet. During the inspection it was indicated that the in process controls were not to achieve a target weight gain for the final coated tablet but merely to monitor volume of solution applied. This approach is inappropriate if registered parameters are not being met.

4.5 The Inspectors continue to support the ongoing upgrade work for [redacted] facility.

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme	✓	N/a	*Continued multiple inspections required at this large site at approximately 6 to 8 month intervals*
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The members of staff detailed above attended the closing meeting. They accepted the findings.

F2 Assessment of response(s) to inspection report

An acceptable response was received (xx/xx/xx).

F3 Documents or Samples taken

Not applicable

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

Overall the site is in control and demonstrates compliance with the requirements of GMP.

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Name and Dated Signature of Lead Inspector:

Signed: [redacted] **Dated:** 27th Aug 2015

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	2	Last inspection:	1
Other deficiencies this inspection:	3	Last Inspection:	4

(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
	Other discriminatory factor (record details and justify below)

(d). Inspectors Comments Related to Discriminatory Factors

This site is a Steriles super site with substantial levels of change including the current building and commissioning of SPP5.

The frequency of inspection is not "elevated" but the site inspection needs on rotation

1. Tablet manufacturing and the warehouse (this inspection)
2. Packaging operation.
3. Sterile area. (SPP5 is due to be commissioned around Dec 2015)

(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

Not applicable

(g). GMP certificate conditioning remarks required as a result of risk-based decisions noted in section (f) above

Not applicable

(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:

Rating:	Next Inspection due by:
[redacted]	

Annex 2

Mon 15th	Tues 16th	Wed 17th		Thur 18th		Fri 19th
Travel Site – AM at 11.30 ish Opening meeting	Change control Transition of the new products Projects	Non sterile [redacted] Other Tabletting Manufacturing facilities Meeting to discuss deviation [redacted]		[redacted] – introduction to new steriles project SPP5	Rachel Batch Review – [redacted] and QP Batch certification	Follow up outstanding aspects Closing meeting
Lunch						
Site update Quality systems Chp 3 5 8 Annex 15	Warehouse	[redacted] Microbiology Laboratory	[redacted] Tabletting cont	[redacted] introduction to new steriles project SPP5	Packaging Follow up outstanding aspects	