Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Quotient Clinical Limited
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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MS / MIA(IMP) 35718

Licence Holder/Applicant: Quotient Clinical Limited

Details of Product(s)/ Clinical trials/Studies: Manufacture of IMPs (sterile, non-sterile and radiolabelled); [redacted]

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	Y
Manufacture of Finished Medicinal Products – Biologicals	N
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
Broker	N
Other: *Formulation Development, IMP manufacture, CRO*	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 13-15 June 2017

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP/IMP 35718/8697-0022

Section B General Introduction

B1 Background information

Quotient has both a MS and MIA(IMP) manufacturing licences. The company is an early phase pharmaceutical development company and involved in several activities namely:

- Formulation development
- Contract IMP manufacturer
- QP certification services for IMPs
- Clinical Pharmacology services
- Clinical data research
- The site inspected also has an 85-bed [redacted] unit with clinical staff.

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Manufacture of IMPs is predominately for the same site with the MS licence being used in a limited way for compassionate supply and the importation of [redacted]
Manufacturing is on a small scale which also can involve [redacted] or [redacted] and bound radiolabelled [redacted] drug products, refer to SMF for a comprehensive list of products being produced.
Dosage forms being manufactured are [redacted]. All products have short shelf lives applied therefore no sterility testing is conducted for sterile products.

During the initial planning of this inspection, it was intended to include a new satellite manufacturing site at [redacted] in Nottingham within the scope. Unfortunately, this facility was subject to flooding shortly before the inspection and therefore significant remedial action will be necessary before the facility will be inspection-ready. The company confirmed that progress with this or any change in plans would be communicated to the inspectors.

Previous Inspection Date(s): 26th(pm) to 29th(am) August 2014 (three days)

Previous Inspectors: [redacted]

B2 Inspected Areas

Introductions, site overview, changes, future plans, completion of actions from last inspection review of licences.
Quality System: management review, PQRs, complaints, recall, deviations, CAPA, change control, technical agreements, TSE, vendor assurance, OOS, labelling, batch records, release procedures, VMP, sterility assurance, calibration, maintenance, training, self inspection, pest control.
Facility Tour: storage areas, dispensing, manufacturing, packaging, QC laboratory

Limitations / exclusions to inspected areas

- Parenteral manufacture was not observed.
- Dispensing activities were not observed.
- Validation systems were not reviewed in detail.

Items that may be of interest at subsequent inspections:

- HVAC system faults and servicing
- Human error rates.
- Label generation and error rate.
- Changes to the media fill approach from study specific to a bracketed approach.

B3 Key Personnel met/contacted during the inspection

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[redacted]

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[redacted]

* Present at closing meeting

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	Version 11, May 2017	Yes
Compliance Report	Dated 05th June 2017	Yes
Comments: Not applicable.		

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:

- An expansion to the Trent House GMP facility had been made, incorporating a goods-in / quarantine store, an additional GMP store, packing and label rooms and an external equipment store.
- The laboratories had been moved from Sherwood House to Lime House.
- [redacted] had been implemented.
- [redacted] system had been implemented.

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

- The company was in the final stages of selecting an [redacted] – anticipated decision in summer 2017.
- The company was also in the early stages of evaluating electronic materials management systems.
- The satellite facility at [redacted] was not ready for inspection due to a flooding incident. The company was reviewing their options for the expansion and will continue to keep the Inspectorate informed.

C2 Action taken since the last inspection

Actions from the previous inspection had generally been addressed.

C3 Starting Materials

General

Starting materials were assessed and released by QC and obtained from approved suppliers. An approved supplier list, with brokers was generated and approved by QA.

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Radiopharmaceutical generators were checked for [redacted] and [redacted] breakthrough on receipt from authorised suppliers.

[redacted] used to radiolabel IMPs was supplied by the [redacted]

Raw materials were assessed on an individual basis per project, even if other materials had previously been sourced from the same supplier. A risk assessment template form was used for each material; examples were reviewed [redacted] and found to be comprehensive.

Compliance with TSE Guidelines

There was a full assessment of the risk of TSE during a new trial introduction as part of the pharmaceutical development control strategy. This was described in [redacted] and was compliant with the TSE guideline.

API Compliance

The sponsors were responsible for ensuring the supply of any APIs and ensuring that APIs were manufactured in accordance with GMP. This process was a requirement of all technical agreements and relevant documentation was assessed and checked by QA.

C4 Pharmaceutical Quality System

General

A Quality Management System was present but not comprehensive in many areas such as investigating and effectively resolving quality issues, customer complaints and change control. A major deficiency was raised during the inspection in relation to these areas including customer complaints and quality incidents, refer to section D.

The Quality Assurance Department was involved in monitoring compliance in all areas of the operations. They were responsible for review of documentation prior to final product assessment, for investigation of deviations, for change control and for organisation of validation programmes. Final disposal of materials and products was controlled by QA and was independent of production.

The quality management system was a paper based, manual system with procedures having a two-yearly review frequency.

A system was in place for keeping up to date with regulatory changes [redacted] with designated personnel assigned to monitor for these. A gap analysis had been conducted for the revision to Annex 16, however this was only approved in January 2017 which was later than the effective date of April 2016.

Periodic Quality Reviews

There was a process of periodic quality review (PQRs) which covered different dosage types for investigational medicinal products.

Periodic quality reviews were produced annually, in accordance to a quality policy [redacted]

PQR records for 2016 were reviewed and these were satisfactory, identifying areas of improvement and associated recommendations.

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There were four dosage areas that the PQRs cover: [redacted]

A lot more [redacted] was manufactured than parenteral IMPs, with drug in bottle being the biggest dosage form being supplied.

There was a high degree of manual processing in production, which has led to a number of quality issues being related to "human error". The effective resolution of "human error issues" was discussed with the site team. Quality issues related to human error may be of interest at the next inspection.

A monthly quality management review process was in place and there was a review of quality metrics, however effective identification and management of any adverse trends was limited.

New Product Trial introduction.

Introduction of new clinical trials was well controlled with a project management team to organise the requirements of the regulatory aspects including compliance with Annex 13 and GMP. There was a QP assigned to each project and they play a pivotal role in the team. The roles and responsibilities together with other members of the team were defined in procedure [redacted] The new trial introduction was a process which controls the study start up, study delivery and study close out.

The QP had responsibility for overseeing the completion of the risk and impact assessments as well as authorising the product specification file, Technical Agreement with the [redacted] and ensuring that all documentation related to the Ethics Committee and MHRA trial authorisation process has been completed prior to release.

The four project management teams worked actively with the respective [redacted] to deal with any issues or with the sponsoring organisation.

The roles and responsibilities of the sponsor were defined in detail including the supply of any API and declaration of manufacture with regards to GMP standards.

There was a defined process of managing third parties or external organisations when a new trial is being initiated and assessed.

A pharmaceutical development plan [redacted] and control strategy was developed and was the framework by which the following assessments were conducted:

- Product quality risk assessment
- Critical quality risk assessment
- Cleaning verification
- Process development
- Packaging design
- QC testing methods
- Stability
- Contamination control
- Documentation and reporting

Supply to external organisations, shipping and packing configuration requirements were controlled by the procedure, [redacted]

Quality Incidents

Quality Incidents (QIs) were governed by the procedure [redacted] and were classified as either major, minor or observation. Any serious breach of GCP or study protocol was escalated immediately to the QA Management. Principal Investigators were notified by QA of all QIs and

were responsible to review all QIs in relation to the study especially related to any impact on subject safety and or data integrity.

QPs reviewed QIs as part of the assessment process, together with the investigation and finally authorising the QIs. If there was a serious breach of protocol or GCP and or defective product/ complaint, then these were dealt with by separate procedures. The QI procedure was silent in relation to the requirement to support conclusions to risk assessment, communication with QPs; Investigators and Sponsors.

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The procedure related to implementation of corrective and preventative action (CAPA procedure [redacted] did not have an effective system to check CAPA effectiveness and justification if human error was cited as a root cause.

QI records reviewed: [redacted] in relation to the [redacted] subject been labelled with the wrong subject number (an active subject) for the [redacted] batch [redacted], dated 19th December 2016 subsequently the active was also labelled incorrectly. The investigation was thorough and most CAPAs were robust however the [redacted] was not performed in a timely fashion. This CAPA was in relation to performing the risk assessment for label generation checking and the overall control process in order to identify failure modes and perform appropriate CAPAs. This essential CAPA had still not completed by the time of the inspection and the due date for completion was June 2017. The timelines were excessive for the severity of the QI and the fact that other labelling QIs had occurred. This and other QIs had not been effectively challenged by approvers.

Other QIs reviewed were: [redacted].

Change Control

[redacted] described the process for change control and included both permanent and temporary changes within the scope. Effectiveness checks were included as part of the change control closure (effective implementation as planned) and there was also provision to include subsequent checks within the CAPA system or as part of the internal audit procedure.

A selection of change control documents was reviewed and whilst most individual examples were generally acceptable, several issues and inconsistencies were noted; refer to section D. Changes reviewed: [redacted].

Validation Master Plan

The VMP was implemented as a policy document [redacted] and covered equipment (both GMP and GCP), facilities, manufacturing processes (aseptic and cleaning), analytical methods, computerised systems, spreadsheets, trial data validation / verification and validation activities conducted by sub-contractors.

Validation systems were not inspected in detail and may be of interest at the next inspection.

C5 Personnel

The company had an appropriately qualified and experienced management team.

Appropriate numbers of adequately qualified and experienced staff were available for all functions. There was an acceptable commitment to training.

There had been an increase in overall total staff headcount from 221 to 338 since the previous inspection. The majority of these staff were however not involved in GMP manufacturing activities.

C6 Premises and Equipment

These were adequately described in the site master file. They were mostly unchanged since the previous inspection except for those items and additions noted under “changes” above. General

house-keeping was good with satisfactory workflows and effective segregation of operations, with the exceptions of deficiencies noted in section D.

There were several buildings spread over the site, refer to the site master file (SMF)

The GMP manufacturing area was located on the first floor of Trent House, refer to the SMF for the floor layout, room grades, equipment list and information on utilities.

Starting materials were received in Sherwood House, initially checked and verified then sent to Trent House to be processed and assessed further.

Further checks on certificates of analysis and documentation were made against the relevant approved suppliers list, then the stock was booked in using the MMD system (material management database). The stock was assigned a status, then stored in the Goods Store.

Appropriate pest control measures were evident in all areas.

Goods Store:

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The area was organised, with materials managed in accordance with procedures and GMP. Materials were assessed by QC and then the status was changed from unapproved on receipt to approved and released. Material status was indicated by stickers and on the MMD system. Checks made on the MMD system, starting materials status, against the [redacted] were satisfactory. Temperature monitoring was 24/7 with [redacted] sensors at the time of the inspection. Two freezers were present and satisfactory, all fridges were pharmaceutical fridges, again with sensors and readings indicated a good level of control.

A sampling booth existed in the goods store but this was being used both as a sampling booth and for testing excipients. APIs were sampled and tested in GMP4, which was discussed with the site; they were asked to review this practice in order to determine further control measures to reduce cross-contamination.

Equipment Store

The equipment located in the store room was stored in a clean state, labelled with appropriate status and equipment log books were satisfactory. Tablet tooling was checked and was stored, tooling logs were satisfactory. Once tooling was been made for a trial it was then disposed of once used.

GMP Store 2

This was where the retained samples were being stored. This area was satisfactory with retained samples being stored in a well-controlled manner, with full inventory and appropriate GMP documentation, traceability and monitoring of conditions.

Dispensing Operations:

None were observed during this inspection and may be of interest to observe at the next inspection. Dispensing activities if required occurred in the actual GMP production rooms for that IMP trail. The trail was a discrete production operation with cleaning and cleaning verification together with effective change over procedures between production of different IMPs.

Packaging Room:

This was well ordered, small but adequate for the size of the operations. There was effective segregation and status labelling of the room, locations and bays. The rooms were temperature controlled and monitored effectively. Room and bay log books were satisfactory with effective pre-and post-clearance checks.

Production Clean Rooms

Manufacturing was small scale with the following limited activities being observed during the inspection:

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GMP 4: [redacted] study [redacted]

GMP 5: [redacted], study [redacted]

GMP 1,2,3 were used to produce sterile parenterals using closed procedures. Parenteral production was not observed during this inspection but was discussed.

Clean room fabric and condition were compliant with EU GMP Annex 1. There was a risk of contamination due to a lack of control measures and changing practices since an unclassified changing room together with the main corridor led to grade C rooms. This was raised as a deficiency (refer to section D). The changing procedure did not reduce the risk of contamination into the grade C areas.

Isolators were in satisfactory condition with appropriate checking of condition, leak testing of gloves and pressure checks on a daily and weekly basis.

Pressure cascades were satisfactory and complaint with EU GMP Annex 1, although some of the pressures were at the lower acceptable limits.

Sporicidal and antibacterial sanitising agents were being used in a two-stage transfer process.

Service and planned preventative reports were acceptable for the rooms and isolators, demonstrating compliance with grade C and grade A conditions.

Environmental Monitoring

An appropriate monitoring programme was in place. Quarterly trending of data was performed for both viable and non-viable particles. The reports from [redacted] and [redacted] were reviewed and demonstrated the facilities to be generally in control. It was noted that the non-viable particle limits used were tighter than those defined in EU GMP Annex 1.

Labelling Room

There was a [redacted] printing system in place label production and generation was checked. Approved master labels were not locked when saved and were stored as unsecured MS Word documents; this was discussed with the site and raised as a deficiency.

Performance qualification, calibration and linearity tests for [redacted]) dose calibrators.

Records for performance qualification, calibration and linearity including test methodology were acceptable. There was however a concern in relation to the fact the Excel spreadsheet used to determine calibration had two versions and was in fact not qualified; a QI had been raised. There was a lack of audit transparency that the calculations used to determine activity and hence the accuracy of calibration results had been verified as part of the investigation into the QI. That historical calibration and qualification data had been checked as part of the investigation to determine the impact of the error. During the inspection, the company was able to demonstrate the above considerations and exercises had been performed but the audit trail of events, impact assessment and retrospective checks were poorly detailed within the QI.

C7 Documentation

Documentation was reviewed in relation to the inspected areas [redacted]

There was a comprehensive documentation system in place to document all aspects of the quality management system. Procedures and other documentation were reviewed, controlled and managed effectively, however examples were seen of the use of 'pp' signatures with no formal control or policy in place for this.

Areas of the documentation system that were unsatisfactory are referred to in section D of this report.

Product Specification File (PSF) generation was reviewed and was well controlled with a procedural and systematic approach. Final approval and authorisation was by QA and the trial

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QP. The process and parts present in the generation of the PSF were complaint with Annex 13 and included items such as: [redacted] trial authorisation number, amendments and restrictions, ethics approval, technical agreements with [redacted], IMP and API product and labelling details, randomisation, blinding and un-blinding processes. The PSF process and related procedure also included processes to handle emergency situations, (communication stream with relevant parties, regulators, un-blinding operations). Amendments to trials were also controlled by a procedure [redacted] Remote QP certification and release of IMPs was not a company practice.

Batch documentation and QP release were reviewed [redacted] and found to be well controlled and compliant.

Generation and use of SOPs and batch records were described in [redacted] and [redacted] and were generally acceptable.

Data governance policy [redacted] had been implemented in November 2016. This made reference to the requirements of EU GMP Annex 11 for computerised systems but was lacking in detail for paper-based systems. This was discussed with the site.

C8 Production

Production was small scale with manual manufacturing and packaging methods being employed. Tablets were produced on an individual tablet press or a semi-automated [redacted], capsules were hand filled.

Processing was in accordance with procedures and with the procedures and records were maintained acceptably. In-process testing practice and results were acceptable.

Cross-contamination control and cleaning verification:

Most of the equipment used in production was disposable or contact parts were dedicated to the IMP trial and disposed of afterwards, for example sieves and tablet tooling were all dedicated.

There was a full assessment of the risk of cross-contamination during a new trial introduction as part of the pharmaceutical development control strategy.

The API was fully assed in relation to: type of molecule, COSHH, toxicology, TSE, solubility, potency, microbiological contamination, impact on rooms and equipment train, effect on placebo. The cross-contamination control and cleaning verification processes were complaint with GMP and Annex 13 requirements.

The stability and degradation of the API was also considered and this information was sought from the [redacted] if known.

After each production of an IMP cleaning verification was conducted. Records of cleaning verification, cross-contamination risk assessments, were reviewed and found to be acceptable with acceptable residue limits calculated, tested and applied.

Media fills

Aseptic process validation and operator validation were covered by [redacted] and [redacted] respectively. Broth transfer trials were used as part of verification of operator technique and study-specific media fills were conducted in triplicate prior to each project requiring aseptic manufacture. There were study-specific 90 media fills conducted in 2016 with no failures reported.

The process in place at the time of inspection was for each operator was required to successfully complete three broth transfer trials and be involved in at least one of the three types of study-specific media fills prior to being considered qualified.

It was discussed that the company were considering the use of routine bracketed media fills for vial-filled products. A comment was raised in relation to this and the change may be of interest at the next inspection.

C9 Quality Control

Analytical laboratories

Since the previous inspection, the laboratories had been relocated from Sherwood House to a fully refurbished area in Lime House. The laboratories were orderly and had a logical flow to activities. Approximately 25 staff worked in the laboratories, with a split of 10 development and 15 QC staff, however all were subject to GMP training and all equipment was qualified to GMP standards. Dedicated analytical coordinator and data checker roles had also been implemented since the previous inspection.

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The company had implemented a [redacted] data acquisition system and [redacted] of the [redacted] systems [redacted] were connected to the system. The two systems that were not connected (systems [redacted] and [redacted]) were clearly identified for development use only. The use of the system and access levels were discussed in detail and several issues were identified; refer to section D.

Eight dissolution bath were available, with a six-monthly external calibration.

Reference standards were managed within the materials management database and appropriate storage conditions were available.

Sterility testing

A baseline risk assessment document was available regarding the short shelf life applied to all products and therefore the absence of the use of a sterility test for parenteral products. This was prepared in August 2015 and included a good level of detail.

Reference samples

It was stated in policy document [redacted] that reference samples were the responsibility of the [redacted] and the [redacted] would not take samples unless specifically requested by the [redacted]. This did not take into account the requirements of Annex 13 regarding storage of reference samples within an EEA / MRA country unless otherwise justified; refer to section D.

C10 Outsourced Activities

Assessment of subcontractors and key suppliers was describe in [redacted] This described that the initial re-evaluation was conducted two years after first approval and every three years thereafter.

It was noted that the risk assessment process permitted 'high severity / low occurrence' to be assigned an overall low risk with no action required despite a failure mode of 'high severity' being identified.

Quality Agreements were described in [redacted] with a Quality Agreement generated for each client and Technical Addendums implemented to the agreement for each study conducted. A template agreement was available which was generally comprehensive however there were several cases where the responsibilities were assigned to both the contract acceptor and contract giver, suggesting that further detail may be required. The procedure included a requirement that if a client template was used, that a review against [redacted]s template should be performed to ensure the minimum required information was included.

Several agreements and associated assessments / audit reports were reviewed. These were generally comprehensive however the details held on file for [redacted] (supplier of licensed products) were incomplete when reviewed against the details on the EudraGMDP database. In addition, the risk form associated with [redacted] (IMP

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manufacturing site in the USA) was not clear regarding what the site was approved for. The audit report for [redacted] (contract testing laboratory) included appropriate detail.

C11 Complaints and Product Recall

Complaints and recalls were governed by the procedure Complaints, suspected defective products and product recall ([redacted]) which at the time of the inspection was not compliant with the requirements of EU GMP Chapter 8; refer to section D.

QA investigated the complaint and report to the trial QP, if there was a requirement to liaise with the MHRA in relation to a possible recall then the QP would also be part of this process.

Customer complaints were reviewed and resolved in a timely manner.

Complaint records were comprehensive and appropriate where investigations had been performed with resulting corrective actions implemented. There was a lack of evidence to demonstrate that customer complaints had been reviewed to determine reoccurring quality or product specific problems.

The recall procedure and systems in place were periodically challenged.

There had been two recalls issued from this site since the last inspection – initiation dates [redacted] and [redacted]. [redacted] was due to black particles found in [redacted], which appeared to be plastic in nature. [redacted] was related to fibres found in the product. The investigations were thorough and determined root causes however, there were no overall comprehensive reports in relation to these recalls and this was raised as a deficiency; refer to section D. Evidence of timely communication with the MHRA, other regulators, sponsors and investigating sites was satisfactory.

C12 Self Inspection

A self-inspection programme was in place as detailed in [redacted]. The company's schedules were generally being adhered to and the procedure included relevant areas to be considered, including not just compliance with procedures but review of those procedures to ensure compliance with relevant GMPs.

C13 Distribution and shipment (including WDA activities if relevant)

IMPs manufactured were primarily used in the clinic on site, however a small number of products were sent to other sites. [redacted] described the requirements for shipping IMPs off site and included appropriate details regarding maintenance and monitoring of appropriate temperature conditions during the transfer.

Example shipment documentation relating to study [redacted] were reviewed and no specific issues were raised.

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 The pharmaceutical quality system was deficient in that:

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2.1.1 The system for managing Quality Issues [redacted] was deficient in relation to the following areas, as evidenced by QI reports [redacted]

2.1.1.1 There was no requirement to be able to reproduce a complete audit trail of events for more complex or major Quality Issues (QIs)

2.1.1.2 The procedure was silent in relation to extent and evidence required to produce and support a detailed impact assessment and assessing the degree of risk to product, batches, trials, subjects and supporting evidence to justify the final decision.

2.1.1.3 There was no system to demonstrate that corrective and preventative actions were effective and completely traceable (some CAPA were given a N/A not a number)

2.1.1.4 There was a lack of detail and clarification of when and how QPs [redacted] (when required) are communicated with.

2.1.1.5 The QI records referenced were not appropriately challenged by the approvers.

2.1.2 The complaints, suspected defective products and product recalls procedure [redacted]) was not updated in line with current chapter 8 requirements, for instance it was lacking with regards to:

2.1.2.1 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

2.1.2.2 The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.

2.1.2.3 The decision-making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.

2.1.2.4 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

2.1.2.5 There were no comprehensive recall reports aligned to chapter 8 requirements for the recalls initiated on the 15/12/2015 and 6 /6/2015.

2.1.3 Management of change control was deficient in that:

2.1.3.1 Temporary changes were not appropriately managed in accordance with procedures. For example, [redacted] was raised on 02 Mar 2017 with an estimated validity period until May 2017 however this was closed on 03 Mar 2017 and it was not clear how this had been tracked within the quality system to ensure that the relevant process had returned to its normal state.

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2.1.3.2 Prospective evaluation of changes was not consistently documented. For example, [redacted] included target and actual completion dates for actions in March 2017 however the form was not signed as 'approved in principle' for execution until 12 Jun 2017.

2.1.3.3 [redacted] included a comment on 11 May 2017 that the change was to be closed and superseded by [redacted] which was raised at that time. [redacted] however remained open at the time of inspection in June 2017.

Reference: EU GMP Part 1, Chapter 1 (1.4 viii, ix, xii, xiv; 1.8vii), Chapter 8 (8.9i-ix, 8.10, 8.13, 8.28, 8.29)

3 OTHERS

3.1 Management and control of computerised systems and documentation practices was deficient in that:

3.1.1 Several generic user accounts were present within the chromatography data acquisition system resulting in any activity under these profiles not being attributable to individual users. For example, [redacted]' and [redacted] within the top-level administrator accounts and 'Test one' within the laboratory administrator accounts.

3.1.2 The Senior Director of Analytics held administrator level access to the chromatography data acquisition system which was considered a conflict.

3.1.3 There was no periodic review of system audit trails.

3.1.4 There was no periodic check for unreported data within the chromatography data acquisition system, with only the submitted analyses formally reviewed.

3.1.5 The Word documents present in the label production computer terminal i.e. label production sheet [redacted]) were saved as "read only" but the documents were not locked.

3.1.6 Examples were observed of the use of 'pp' signatures in change control and deviation reports however there was no policy or control relating to this practice.

Reference: EU GMP Part 1, Chapter 4 (Principle, 4.3, 4.8); Annex 11 (1, 12, 14)

3.2 There was a risk of contamination to clean rooms in relation to gowning and changing practices. For example:

3.2.1 The change room was an unclassified area together with the main corridor which fed grade C clean rooms, there were no control measures in place to reduce the amount of contamination through process flows.

3.2.2 There was no two stage change in order to gown into grade C clothing for grade C areas.

3.2.3 During the inspection it was observed that the gowning process allowed the wearing of outdoor shoes and clothing under grade C garments.

3.2.4 Grade C Clean room clothing was being changed into on the "dirty side" of the step over bench

Reference: EU GMP Part 1, Annex 1 (44, 45, 64)

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3.3 Vendor assurance was deficient in that the information available to support the approval of [redacted] (supplier of licensed products) was incomplete in that it did not include a current GDP certificate and the address on file appeared to only cover part of the licensed company when cross-checked against the EudraGMDP database.

Reference: EU GMP Part 1, Chapter 5 (5.27)

3.4 There was no formal process within the quality system to ensure reference samples of IMPs manufactured in third countries were taken and stored within the EEA.

Reference: EU GMP Part 1, Annex 13 (37)

3.5 With respect to facility control:

3.5.1 There was no dedicated, secure and labelled returns or recall area for recalled or returned trial stock.

3.5.2 Within the log book in relation to documenting daily trends ([redacted] issued 1st May 2017) actual readings were not recorded together with stated acceptable limits. There were repeated excursions with relative humidity and low pressures with no reference to any investigation or QI, with only statements of 'no action required'.

Reference: EU GMP Part 1, Chapter 3 (3.3, 3.23)

3.6 With respect to management of radiolabelling activities:

3.6.1 There was a lack of justification for the acceptance criteria or limits that are being used for radioactivity linearity tests.

3.6.2 There were no defined acceptance limits for the radioactivity checks on generators when compared with a calibration chart.

Reference: EU GMP Part 1, Chapter 6 (6.19, 6.20); Annex 3 (20, 31, 36)

4 COMMENTS

4.1 It was discussed that the procedurally stated archival period of 5 years after trial completion for Trial Master File documentation should be reviewed in line with GCP requirements as necessary.

4.2 The company's approach to media fill validation for vial-filled products was under review at the time of inspection to move from project-specific validation to a bracketed routine approach. While the inspectors had no objection to the proposals in principle, it was discussed that the company should consider the impact to the more infrequently produced aseptic presentations such as product in bags and the current practice of declaring these media fills as prospectively valid for six months.

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]	[redacted]
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The closing meeting was held with individuals listed in B3 and the deficiencies were verbally accepted in a positive manner. The company committed to addressing the issues.

F2 Assessment of response(s) to inspection report

A response was received on 13 Jul 2017 which was generally comprehensive. Additional clarification for several points was requested from the company on 14 Aug 2017 and further responses were received on 18 Aug 2017 which were deemed to be satisfactory.

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F3 Documents or Samples taken

Electronic copies of the company presentation, form [redacted] (PSF Document Review Checklist) and a list of studies from 2014 to the time of inspection have been saved to the inspection case folder.

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	N/A
GMP as required by HMR 2012 (as amended)	✓
Directive 2001/20/EC	✓
Directive 2001/82/EC	N/A
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	N/A

and is acceptable for the products in question.

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Name and Dated Signature of Inspector (s):

Signed: [redacted] **Dated:** 18 Aug 2017
Name:

Accompanying Inspector: [redacted] **Dated:** 18.08.2017

Name:

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	1	Last inspection:	1
Other deficiencies this inspection:	6	Last Inspection:	8

(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)

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(d). Inspectors Comments Related to Discriminatory Factors

[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	

(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):

[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