Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

ITH PHARMA LIMITED
UNIT 2 & 4
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NW10 7NZ

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: This was a routine re-inspection to confirm compliance with GMP

Licence or Reference Number: MS, Man SA, WDA(H) (for unit 4 only)

Licence Holder/Applicant: N/A

Details of Product(s)/ Clinical trials/Studies: The site manufactures [redacted].

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	Y
Manufacture of Finished Medicinal Products - Biologicals	Y
Manufacture of Intermediate or Bulk	Y
Packaging – Primary	N
Packaging - Secondary	Y
Importing	N
Laboratory Testing	Y
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *E.g. Development, IMP activities, importation of API*	N

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

Site Contact: [redacted]

Date(s) of Inspection: 5 - 7th August 2019 (2.5 days)

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP/GDP 33634/544699 - 0013, Insp GMP 33634-16611523 - 0002

Section B General Introduction

B1 Background information

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This was the first full inspection of the site since September 2016. The last two inspections followed the fitting out of unit 2 and alterations to unit 4. The site is a significant supplier to the NHS for [redacted] and work processes were designed to provide a high output, same day service to customers. The site was originally located in Unit 4 and unit 2 was subsequently purchased and approved for use by the MHRA in 2017. The upper floor of Unit 4 was currently about to be refurbished and was currently not is use. Operations in both Unit 2 and unit 4 were reviewed at this inspection. Unit 2 was designated as the backup facility for unit 4.

Previous Inspection Date(s): 5th November 2018

Previous Inspectors: [redacted]

B2 Inspected Areas

Ordering process
Order entry
Bona Fide checks
Capacity plan: review and adjustment, deviations

Quality system
Deviations, complaints, recalls, change control
Rejected batches review
Batch records

Manufacture
CCTV review unit 2 and 4
Cleaning, disinfection and transfer
iHP use
Line clearance
Control of [redacted]
Use of ICAP, test bags, significant changes
Compounding
Visual inspection, labelling and packing
General cleanroom Cleaning and Contract cleaners
Batch release

Monitoring
Continuous particle monitoring and FMS system
Environmental Monitoring strategy
Process validation – media fills and failure review
Sterility testing/ end of session monitoring
Microbiology –GPT, ID, excursions and reporting
Smoke testing

Others
Self-inspection
Maintenance/FMS system

Control of SOP TSE Data Integrity controls Product stability/expiry date justification Training/ Cross training of personnel Roles of production personnel Distribution to external customers Technical agreements

Limitations / exclusions to inspected areas

Both Units 2&4 were inspection except for the upper floor of unit 4 which was undergoing refurbishment.

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	[redacted]	Y
Compliance Report	Dated 1/8/19	Y
Comments: None		

Section C Inspector's Findings

C1 Summary of significant changes

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

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

The following changes have occurred since the last inspection:

- Production volumes have increased.
- There have been various personnel changes with the QA manager leaving in August 2018.
- There has been a 10% increase in staff to 220 in total.
- [redacted] has moved to unit 2 whilst the upper floor of unit 4 was being refurbished.
- A new microbiology lab with [redacted] indicator testing using a [redacted] and a new database for EM results. A [redacted] was purchased for in-house species Identification of microorganisms.

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- Systems such as [redacted] for worksheet design, [redacted] for personnel monitoring and [redacted] for warehouse management linked to SAP have been introduced. (SAP went live at the inspection)

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

The following changes are planned:

- The upper floor of unit 4 will be refurbished with enlarged cabinets for working, [redacted] and was due to be completed at the end of January 2020. Once the work is completed, a summary report was requested and MHRA would aim to perform a remote assessment of the upgraded floor.
- A new Quality Event (QE) system accessed through SAP will be introduced.

C2 Action taken since the last inspection

Actions had been addressed.

C3 Starting Materials

General

Not applicable as licensed or unlicensed products are only used.

Compliance with TSE Guidelines

A TSE statement was present on the certificate of conformance of each unlicensed product.

API Compliance

N/A

C4 Pharmaceutical Quality System

Quality Events

The quality event [redacted] which included errors initiated by customers, operators themselves and training errors was reviewed. A quarterly trend report was prepared to identify reoccurring errors. Timelines for each error type were defined e.g. critical errors should be addressed within 24 hours with the line manager and quality informed immediately. There was an extension scheme for delayed completion of actions however it was not clear how many extensions were allowed by the QA manager. QE were recorded in an excel spreadsheet and approved by the production manager and quality manager.

In the SOP, an 'other' QE was mentioned but it was unclear what this meant. A risk assessment and root cause analysis were performed for each QE, however a CAPA effectiveness check was not currently done. One of the main QE's types seen was for contamination e.g. hairs on components which may be overreported. If there was a spillage on a compounder, it would be stripped down, and the assembly started again from scratch.

Various QE were selected for review: [redacted] for [redacted] lot [redacted] set up where there was a shortage of [redacted] and [redacted] was drawn up into a [redacted] prior to obtaining additional product. The batch was discarded; [redacted] for a double addition error in [redacted] A new method of preparation was written; [redacted] for leakage in a non-vented inlet on a compounder. The set up was taken down and [redacted] did not find a fault in the manifold; [redacted] for a hair found on a [redacted] The hair was placed on a settle plate to detect any microbial growth; [redacted] for a batch which was processed with the incorrect amount [redacted] instead of [redacted]) of [redacted] due to workload pressures and was discarded; [redacted] for the wrong strength of [redacted] used ([redacted] This incident was reported at the

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compounders meeting so that all personnel were informed; [redacted] for a settle plate not being exposed in the cabinet due to distraction.

A further review of QE for compounder set-up failures indicated that 16 incidents were recorded in the last year. [redacted] and other examples for mislabelling of configuration bags which resulted in all produced bags being discarded. If two bags fail in a row [redacted] for the operation of the [redacted] the bags produced at risk, until the results were available, were discarded.

Change Control

[redacted] described the change control process and was applicable to both permanent and temporary changes, however the scope of the procedure did not specifically mention temporary changes. In addition, there was no provision with the procedure or form to positively verify that the original state was returned on completion of a temporary change. There were specific forms and process flows for more common types of change, which provided structure to these processes. These included: new products; new products on [redacted] new customers; [redacted] customer templates; [redacted] projects.

The process for approving new customers was generally comprehensive, however was it not clear what would be required other than a check that the company existed if the customer was not a registered healthcare professional / organisation.

Several examples of change controls were selected for review:

- [redacted]. Temporary use of [redacted]
- [redacted]. Rejected change.
- [redacted]. Transfer work back to Unit 4 following refurbishment. Some action completion dates appeared to be typed entries dated after the initial approval signature was applied. In addition, the original copy of this record was not available at the time of inspection, with a copy of the document present in the file.
- [redacted]. Review how to deal with particles in grade A&B areas.
- [redacted]. New customer.
- [redacted]C dated 15/3/19 for [redacted] was reviewed and the associated [redacted] as the dose requested by the customer was incorrect and not detected at the final check. In addition, the stability folder did not indicate that preservative free product should be used.

Quality Management Review

There was a quarterly operations meeting which included quality information but no SOP which covered the quality management review process on site which was raised as a deficiency. There was also a weekly huddle meeting.

C5 Personnel

The list of authorised checkers [redacted] was reviewed and it was noted that operator [redacted] was suspended and the training record of [redacted] for final checking was therefore reviewed. Training was performed by a dedicated team of 5 trainers, took around 9 weeks, and included introductions to GMP [redacted] and [redacted], cleanrooms, formulations, calculations with questions to assess understanding at each stage. A minimum of 100 final product checks were performed as part of training with the error codes for trainee and checker recorded on a form. Once this was completed and the trainee assessed as competent to succeed, a mock test, using mistakes in worksheets, was performed. To pass, the checker was required to have no major errors, 3 minor errors and 3 observations. For [redacted] the mock assessment was passed on 2/5/18 with the final assessment performed on 4/5/18. Once [redacted] started to perform final checking of [redacted] it was noted that they did not seem to understand some aspects of [redacted] which raised questions about competence in [redacted] Currently [redacted] was only performing [redacted] checks.

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The training record for [redacted] who was observed manufacturing [redacted] during the tour of unit 4 and was noted to move a hand over opened [redacted] was also reviewed. Training started on 15/4/19 and was completed on 19/7/19. Training for manufacture included reading critical SOP's transfer of components, 25 assessments for assembly and 25 for setting up worksheets, compounding, understanding aseptic dispensing and completing [redacted] manufacturing under supervision [redacted] compounding training was approved on 30/7/19 with the stock [redacted] in SMOF [redacted] manufactured around one week after sign-off which may be relevant to this finding. It was also confirmed that MA who opened three ampoules at a time was also approved to perform product manufacturing on 20/11/18.

The job roles of support assistants, technical assistants, operators, senior operators, principal operators, supervisors and operation managers were discussed.

It was not formally included in the company's procedures that staff should not enter aseptic processing areas if they were unwell or had open wounds etc. It was confirmed that this was included in the company handbook, however it was discussed that this requirement should form part of the quality system.

C6 Premises and Equipment

Data was backed up daily at a separate server in [redacted]. The facility was of an appropriate design and was very progressive in implementing new technology. Compounding of [redacted] was performed in biological safety cabinets which were grouped into two areas with a central change room for access to both areas.

Clean areas were subject to ionised [redacted] sanitisation overnight, with most equipment and starting materials (products) present in the areas on trolleys [redacted] indicators were located around the cleanroom during every [redacted] cycle to provide assurance of its effectiveness. It was however noted that there was no periodic recalibration of the flow meter used to ensure a consistent dose of the [redacted] solution for each cycle.

Smoke visualisation studies had been performed in both Units 4 and 2 and showed good protection of the grade A zones of the cabinets, with appropriate clearance of air in the grade B areas. It was noted however that there were no visualisation studies available which included equipment in the cabinets or simulated processing activities including aseptic connections and processing activities.

C7 Documentation

Batch documentation met minimum GMP standards with components photographed when assembled as a record rather than recording key information such as [redacted] on paper due to the very high throughput of components. This also meant that a full day's production would have to be recalled in the event of a recall for one specific component. Photographs taken for production on 6/6/19 were requested to confirm that the system for recall of documents worked.

Data integrity policy [redacted] was issued on 02 Aug 2019 and was based on the 2018 MHRA guidance. This listed all software and programs used on site and included two checklist forms for recording process reviews and [redacted] checklists. Several examples of these were reviewed and it was noted that no conclusion or summary was included, with proposed CAPA as applicable. It was recognised that this process had been implemented shortly before the inspection and it was discussed that this should be addressed.

Some examples of 'pp' signatures were noted on change control [redacted] however there was no policy or procedure in place to manage this practice.

C8 Production

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Capacity planning was based on establishing a baseline volume of work and monitoring changes by increases in overtime working and other criteria. It was noted that although order handling and production capacity was monitored there was no capacity plan for personnel managing the quality system. i.e. to ensure that QE, change controls, complaints etc were managed appropriately. The site expects to utilise around 80% capacity and the [redacted] system provided quick feedback to move people around to appropriate areas.

The order receipt process seemed robust with orders accepted via fax, email or online. Cut off times for same day supply were in place and no telephone orders were accepted. Some orders from one Trust were presented as examples of where the form design may lead to mistakes. New customer bona fide was confirmed however there was no reconfirmation of this at regular intervals. Homecare [redacted] was also prepared for supply to [redacted] under contract and the process followed the normal order process.

Unit 2

[redacted] and [redacted] was currently being prepared in unit 2 whilst the upper floor of unit 4 was under refurbishment. A separate cabinet was used for antibiotic manufacture. Manual sanitisation was defined in [redacted] The first stage of transfer to the Preparation room used [redacted] from top to bottom with overlapping movement.

Unit 4

The warehouse was appropriately controlled. There was [redacted] and generator backup for refrigerators. Unlicensed products were checked on receipt against the certificate of conformance. It was noted that agar plates were not stored in the correct orientation in the warehouse.

Components and products were transferred to trolleys and positioned to avoid contact with each other before transfer into the unclassified area. Here they were cleaned with compressed air, sprayed with [redacted] and transferred into the cleanroom for [redacted] sanitisation overnight. Currently only a small amount of manual sanitisation was performed. All trolleys were cleaned weekly but there were no records of this for all trolleys.

An operator was observed preparing stock [redacted] for hospitals and it was noted that their hand moved across the top of the ampoule to discard the broken [redacted] When this was pointed out to the accompanying manager, the batch was discarded, and manufacture restarted. The training record of this operator indicated that they had been adequately trained but only approved for this activity one week prior to the inspection. It was also noted that due to the operator's physical characteristics, there was a gap between the bottom of the goggles and the hood and that the settle plate was placed close enough to the filling location.

The set-up of the compounders was reviewed. A manual line check was performed (bar code verification was not used due to the perceived risk of errors). 4 configuration bags were prepared containing different [redacted] and tested using the [redacted] A standard was run every 5th batch. A [redacted] was also tested using a [redacted] Production continued at risk.

The smallest manual addition was [redacted] and the [redacted] were pumped into the bag using the compounder. Mix check reports were printed after each container was changed. The final checking process was reviewed, and it was noted that the inspection of the bag was performed against the background light rather than against a white/black background. The final checks of the order, components, label was recorded on [redacted]

[redacted] for the preparation of stock [redacted] and [redacted] was reviewed. [redacted] adult, [redacted], [redacted] and [redacted] were manufactured in [redacted] and [redacted] twice daily in batches of around 10 to satisfy daily demand for the compounder and for 3-chamber bag additions to ensure use within 4 hours.

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CCTV was used to observe operations in Unit 4 on 29/7/19 and it was noted that the operator opened three ampoules and then withdrew them into a [redacted] rather than opening one ampoule at a time. The quality of CCTV images for unit 2 was poor and definition was lost when zooming into the cabinet however the CCTV system may be replaced in the future. The time of manufacture was written on the [redacted] but this should have been at the time of manufacture of the first [redacted]e rather than the last [redacted]

The risk assessment dated 11/4/17 for use of an intermediate pooled bag was reviewed and it included a count of the number of manipulations for pooling which was less than if polling was not performed. ([redacted] changes against [redacted] and [redacted] changes). We discussed that the site was looking to engage a company to manufacture larger product sizes for pooling or present a proposal to the MHRA for alternative methods of manufacture which could justify a longer shelf life.

C9 Quality Control

A new Microbiology laboratory had been built in Unit 2 and was responsible for all environmental monitoring and incubation of media fills.

Environmental monitoring included the following:

- Finger dabs after every two hours or at change of product.
- Grade A cabinet settle plates every four hours during activity.
- Grade B settle plates every four hours throughout the working day.
- Periodic bare skin finger dabs before and after handwashing.
- Weekly contact plates and active air samples.
- Weekly swab samples of sanitised items in grade A zones.
- Gown monitoring on initial qualification.

Contact plates and finger dab plates included [redacted] and [redacted] in the [redacted] as disinfectant neutralisers. Monitoring plates were incubated at two temperatures, starting with 20-25ºC for three days followed by 30-35ºC for a further three days. Plate readers were not in use within the laboratory and it was recommended that these should be used for consistency. It was indicated that the site was moving to the use of barcoded plates for traceability to locations and this would be interfaced with the [redacted] database system used for recording and trending of microbiological data. This would also result in information not being recorded on the plates with pen, making them easier to read following incubation.

Any isolate recovered from grade A locations was identified to species level, using the [redacted] system in the laboratory. Equipment for automated [redacted] staining was also available. Identification of moulds were sent to [redacted] or [redacted].

The environmental monitoring [redacted] was generally comprehensive, however it was noted that the settle plate limits were described as for two hour exposure and had been halved from the four hour limits stated in EU GMP Annex 1 for grades C and D, and a limit of [redacted] per two hours was stated for grade B, therefore the implied limit for four hours was [redacted] which was greater than the Annex 1 limit.

Trend data for environmental monitoring were reviewed during weekly huddle meetings, monthly trend reviews, quarterly reports and annual reports (beginning in 2018). Data reviewed during the inspection showed the areas to be in generally good control, however it was noted that microbiology personnel performing monitoring, including within the grade A cabinets during operations did not require routine finger dab monitoring.

Excursions were investigated in [redacted] reports. Several [redacted] reports relating to finger dab excursions were reviewed. It was noted that these did not include consideration of the ongoing activity in the cabinet at the time of monitoring, for example if this involved open or closed manipulations. CCTV was routinely reviewed as part of any excursion. Where three events of finger dab excursions were noted for an operator within a one-

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month period, the procedure required intensive broth fills to be performed, however in [redacted] this had not been included as part of the risk assessment and investigation.

End of session media fills were performed by each operator at least weekly. These were designed to include all the types of manipulation that were routinely performed, with four sizes of [redacted] used, plus the transfer of broth from opened [redacted] into an [redacted]. Each cabinet was included at least weekly in the programme. In addition, each [redacted] was run using broth solution through the [redacted] line every day of use. There was however no formal documented rationale for the approach taken for media fills to ensure that worst case manipulations were included, and it was discussed that this would be of benefit when reviewing changes or new processes. Growth promotion testing was performed for each new lot of input broth, following incubation of media fills. The samples were sent to the laboratories at [redacted]

Five [redacted] bags per month were sent for sterility testing (approximately one test weekly). No failures had been reported. [redacted] sampling prior to [redacted] and/or manual sanitisation was also performed monthly.

A [redacted] system was available in the laboratory and it was indicated that the company was working towards introduction of a rapid sterility test method.

Stability data [redacted] for [redacted] from literature sources was reviewed. An expiry date of 84 days was applied based on assay, [redacted] particles which was supported by the literature review. There were no degradation products. Stability data for [redacted] involved testing using [redacted] and other specialised techniques

Stability data was reviewed every 5 years for generic products and every 2 years for MAB's.

C10 Outsourced Activities

Several example technical agreements were reviewed and found to be generally comprehensive:

- [redacted]).
- [redacted] (contract laboratory work for identification and growth promotion testing).
- [redacted] (refrigerated courier service).

In addition, the supplier audit report for [redacted] was reviewed and no specific issues were noted.

Contract cleaners were employed to clean the floors in the preparation areas and unclassified areas.

C11 Complaints and Product Recall

Recall [redacted] described the recall procedure and was generally comprehensive. The procedure required an annual mock recall to be performed, however included provision to exclude this activity if any real recalls had occurred. The last mock recall was performed in 2017 and whilst generally comprehensive, it was discussed that recording the time taken to gather the relevant information may be of benefit to further enhance the challenge and determine the effectiveness of this. Recalls of licensed starting materials had been initiate in 2018 and 2019 therefore no mock recalls had been performed in these years, however the reports for these were limited to a confirmation that the implicated batches had not been used and did not include a review of the effectiveness of the provisions for recall.

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C12 Self Inspection

[redacted] described the annual schedule for self-inspections. This included thirteen audits and the 2019 schedule was almost complete at the time of inspection. It was indicated that second audits of some areas would be performed if deemed necessary.

C13 Distribution and shipment (including WDA activities if relevant)

[redacted] were used for overnight delivery using refrigerated vehicles. Local couriers were used for same day deliveries, mainly to [redacted], which were not temperature controlled however refrigerated bags were placed in each carton to ensure that the bags remained cool. It was noted that there was no minimum time for storing the bags in the refrigerator prior to use.

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

N/A

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

D1 Critical - None

D2 Major

2.1 Aseptic operations were not sufficiently controlled and monitored as evidenced by:

2.1.1 An operator was observed to move her hand over the top of a [redacted] after opening it prior to transfer to a [redacted] (Note: When this was pointed out to management, the batch was immediately discarded)

2.1.2 An operator was observed on the unit 4 CCTV record from 29/7/19, opening three [redacted] at a time and then withdrawing the contents rather than opening one [redacted] at a time as required in [redacted] for preparing [redacted] and [redacted]

2.1.3 The goggles of one operator who was [redacted] for [redacted] were not fitting correctly resulting in a gap at the bottom of the goggles.

2.1.4 The expiry time written on intermediate [redacted] used for additions to 3 chamber bags started from the end of manufacture rather than from the start of manufacture.

2.1.5 An operator was observed to put on the cleanroom suit before the hood which would lead to a higher level of contact with the suit and increased risk of contamination. This was not in accordance with the current procedure as described. [Note: the operator was requested to re-gown by management prior to entry].

2.1.6 The settle plate in the biosafety cabinet was not sufficiently close to where [redacted] contents was being transferred into the [redacted] to effectively monitor the conditions during manufacture.

2.1.7 The site limit for weekly grade B settle plates was [redacted] per 2 hours therefore the implied limit of [redacted] per 4 hours was not in accordance with EU GMP Annex 1.

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2.1.8	Microbiology personnel who performed routine environmental monitoring were not required to have glove monitoring, despite performing monitoring in the grade A cabinets.
2.1.9	[redacted] required repeat broth testing if three glove monitoring excursions occurred in a one-month period, however this was not done in [redacted].
2.1.10	[redacted] reports for glove monitoring excursions did not include any consideration of the type of manufacturing activity performed during the work session to assess the risk for the product, for example whether this involved open or closed manipulation.
2.1.11	There was no requirement to ensure all cleanroom chairs were fully extended to their maximum height prior to the daily ionised [redacted] sanitisation to ensure that all surfaces were subject to the sanitisation process.
EU GMP	A1.8, A1.18, A1.41, A1.42, A1.64

D3 Others

3.1	The quality system was deficient as evidenced by:
3.1.1	The quality event (QE) process was deficient as evidenced by:
3.1.1.1	The number of extensions allowed in the quality event SOP [redacted] was not defined.
3.1.1.2	The deviation of an 'other QE when a QE number was issued' was unclear in the quality event [redacted]
3.1.1.3	There was no CAPA effectiveness check mentioned in the SOP form for Quality events.
3.1.2	There was no formal SOP for the Quality Management review activities performed on site.
3.1.3	The change control form did not include a requirement to justify why post-implementation review was not required.
EU GMP	C1.4(xii), C1.4(xiv), C1.6
3.2	Some [redacted] in the warehouse were not stored in the appropriate orientation to prevent condensation.
EU GMP	C6.19
3.3	There was no assurance that the cool packs used for the same day shipment of products were placed in the refrigerator for a minimum time to ensure effective cooling during transport to customers.
EU GDP	9.3
3.4	There was no separate capacity plan for the maintenance of the quality system.
EU GMP	C1.4(viii)
3.5	Documents were not always completed to ensure that all significant activities were traceable as evidenced by:
3.5.1	Change control [redacted] included typed completion dates which were after the date of the approval signature.
3.5.2	The original form for change control [redacted] was not in the associated file at the time of inspection and therefore not available for review during the inspection.
3.5.3	Examples of 'pp' signatures were noted in some documents,

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however there was no policy or procedure in place to control their use.

3.5.4 The procedure and records for weekly cleaning of trolleys used to transfer components/products into the cleanrooms were not clear enough to confirm that all trolleys had been cleaned.

EU GMP C4.8

3.6 There was no formal periodic reverification of customer bona fides. Human Medicine Regulations 2012,167(2)

3.7 The qualification of the facility was deficient as evidenced by:

3.7.1 Smoke visualisation studies did not include any aseptic manipulations or operator interventions to determine the effect of these activities on the [redacted] in the biosafety cabinet.

3.7.2 The flow meter used for confirming the delivered volume of [redacted] to the [redacted] sanitisation system was not scheduled for routine calibration.

EU GMP C3.41, A1.54

D4 Comments

4.1 Plate readers were not in use for inspection of environmental monitoring plates. We discussed that these are recommended to ensure consistent and appropriate conditions to maximise the detection of any recovered organisms on the plates.

4.2 We discussed that although the risk assessment for the use of swabs had identified that 'flocked' swabs provided a higher recovery rate, there was no indication that this type of swab had been considered or implemented for use at [redacted]

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 persons listed in B3 attended the close out meeting and the deficiencies were accepted.

F2 Assessment of response(s) to inspection report

A response was received on 04 Sep 2019 which was generally comprehensive. Additional clarification and information relating to several points was requested from the company on 27th September 2019 and further responses were received on 7th October 2019 which were satisfactorily addressed the deficiencies.

F3 Documents or Samples taken

Documents are in the 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	
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.

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Name and Dated Signature of Inspector (s):

Signed: [redacted] **Dated:** 8/10/19

Accompanying Inspector: [redacted] **Dated:** 4/10/19

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	1	Last inspection:	0
Other deficiencies this inspection:	7	Last Inspection:	2

(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 countersignature for RR II)
	Other discriminatory factor (record details and justify below)

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(d [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]

Section 43

[redacted]

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

Risk Rating:	Next Inspection target date:
[redacted]	

Notes regarding re-inspection and GMP certificate validity

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