Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Great Ormond Street Hospital for Children
Cellular Therapies
Great Ormond Street
London
WC1N 3JH

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA(IMP) 17328, MS 17328

Licence Holder/Applicant: Great Ormond Street Hospital for Children NHS Foundation Trust

Details of Product(s)/ Clinical trials/Studies: Viral and cell therapy

Activities carried out by company:	Y/N
Manufacture of Active Ingredients	Y
Manufacture of Finished Medicinal Products – Non sterile	N
Manufacture of Finished Medicinal Products - Sterile	N
Manufacture of Finished Medicinal Products - Biologicals	Y
Manufacture of Intermediate or Bulk	N
Packaging – Primary	Y
Packaging – Secondary	Y
Importing	Y
Laboratory Testing	Y
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	Y
Broker	N
Other: Specials, IMP Activities	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 4th July 2017

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: GMP/IMP 17328/2091287-0004

Section B General Introduction

B1 Background information

The Cellular Therapies unit is located within the main Great Ormond Street Hospital. The unit manufactures gene and cell therapy for use in both clinical trials but also for use under the site's Special license. There is no HTA regulated work conducted in the facility, or under the control of the Gene Therapy unit management.

All ATMP products manufactured by the facility are supplied ready for use; there is no local washing or expansion of cell therapies.

The facility is spread across 2 buildings; the Camelia Botnar Laboratories (CBL) and Octav Botnar Wing (OBW).

Previous Inspection Date(s): 23rd April 2013

Previous Inspectors: [redacted]

B2 Inspected Areas

Quality System (Change Control, Deviations, complaints and recall, management review)
IMPD/PSF controls
Vendor approval
Batch release / certification
Facility Tour (CBL and OPBEW, including storage areas)
Outsourced activities / Technical Agreements
Environmental monitoring
Sterility assurance and media fills
Batch document review

Limitations / exclusions to inspected areas

Training
Self Inspection
Quality control
There was limited production activity during the inspection. Production in isolators was on-going in the OBW clean room (visibility was limited through viewing panels) and no production took place in the CBL facility.

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]		[redacted]

[redacted]		[redacted]	

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	04 / 5th Sept 2016	Y/~~N~~
Compliance Report	11th January 2017	Y/~~N~~
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:

None relating to compliance. The site had implemented a change in CD34+ products, from fresh manufacture to cryopreservation stages. This gives greater opportunity to perform QC testing prior to release.

[redacted]

C2 Action taken since the last inspection

The response was reviewed and a GMP certificate was issued.

C3 Starting Materials

General

Cell-based starting materials are typically collected outside of the Gene Therapy quality system. These may be sourced from other wards in GOSH, or from other tissue establishments. There was a lack of assurance that external collection sites held the required authorisations

Vendor assurance was not specifically reviewed during this inspection. Specifications and TSE certificates were available for the materials used in [redacted] Starting material audits were in the early phase of implementation, and should be reviewed during the next inspection.

Compliance with TSE Guidelines

TSE compliance was acceptable for the specific materials reviewed during the inspection

API Compliance

Not applicable to cell based therapies.

C4 Pharmaceutical Quality System

A quality system was in place, covering all aspects of ATMP manufacture and control. Work was on-going to merge the Gene Therapy quality system with that of the pharmacy department. Deficiencies were identified with respect to how the transition phase was being managed. It was noted that several of the relevant records required for inspection of the Gene Therapy facility were located in the pharmacy department and took time to collate and present for inspection. This was exacerbated by the lack of a suitable inspection room close to the storage location of the records. Inspection logistics should be considered in the planning of the next inspection and discussed with site representatives early in the planning process.

Change Control

Change control was managed via [redacted] Generally this procedure was acceptable. Examples were reviewed including [redacted] to change the supplier of human AB serum from [redacted] This change control had not been internally approved even though the new supplier was in use. The master change controls were stored within QA with local copies being issued to the relevant departments. Examples were seen where the copies had additional actions added to them which did not reflect the masters. There was no system in place to record these additional actions or to confirm that the master had been updated. It was therefore not possible for the reviewers to have adequate oversight of the actions or to ensure that the all quality prerequisites were considered upon closure.

Deviations

Deviation [redacted] was raised as a result of a Grade A microbiological recovery. However this was raised in May 2016 but not closed until September 2016. Additionally there was no documented root cause.

Deviation [redacted] was raised for a sterility failure on batch [redacted] however there was no disposition documented within the record. Additionally the deviation had taken from 5th July 2016 to 5th October 2016 for approval and the recommendations within the investigation were not captured within the CAPA system.

Deviation [redacted] was raised for a starting material sterility failure. Although the deviation had been approved in February 2017, there was no CAPA, no root cause and the investigation was only available in draft format. This brought into question the validity of the review process.

There was evidence of acceptable investigation for environmental excursions (e.g. [redacted]

Management review occurs monthly, and considers relevant metrics.**C5 Personnel**

Staff task-based training was recorded as SOP-related signature logs.

C6 Premises and Equipment

Personnel access to the CBL clean room was unsatisfactory due to lack of adequate hand washing and gowning areas. Personnel were required to gown in an open access corridor prior to entry into an unclassified office area, as a result of attempts to reduce microbiological contamination. The rationale was requested as post inspection correspondence.

There had been no assessment of incremental change upon maintenance of clean room airflows. The CBL clean room had visible additional holes in the ceiling air grilles, described as being in place to allow the engineers access to remove the grilles. There was a lack of control over material and equipment in the CBL clean rooms. A drywipe board was present (particulate source), and several rolls of paperwork were seen between electrical power supply boxes. These were later confirmed to be wiring diagrams for the power supplies and so had been in place for a significant amount of time. A significant amount of equipment [redacted] incubators, [redacted] was also present, including spare equipment parts.

The alarm to AHU 5 located within the OBW laboratory had been decommissioned however there was no status labelling to support this. On further investigation it was found that this decision had not been recorded or documented within the Pharmaceutical Quality System (PQS). There were also examples of poor facility maintenance in OBW, including air grilles and notices fixed in place using autoclave tape.

The OBW laboratory was located adjacent to an office area. At the time of inspection, a sharps bin containing unknown items was seen within this area.

Gene Therapy staff had insufficient control over product storage areas in CBL. The temperature monitoring of the liquid nitrogen tanks used for ATMP storage was performed by [redacted] with Great Ormond Street Hospital having access to the software for review purposes. The technical agreement with [redacted] was not available during the inspection. The temperature monitoring arrangements were under the control of the Cell therapies staff, and insufficiently visible to Gene Therapy staff and quality system. It was noted that various alarm channels were disabled for incubators and dewars; there appeared to be no formal system to ensure Security of the area was also poor. During the inspection tour the door to the liquid nitrogen room was unlocked, and the dewars within were also not secured. A list of personnel was requested who could access the nitrogen store via the card access system. This returned a list of approximately 150 people including some generic cards such as "Temp 1" and "Temp 2".

HEPA filter integrity testing had been performed of the facility b[redacted]n January 2017. However, the testing was not performed against any specification and was recorded "for reference only".

C7 Documentation

Documentation reviewed was of an acceptable standard. Issues were noted during the inspection where control over local copies of procedures, and use of ad-hoc instructions (post-its, white boards etc) were raised as deficiencies. The [redacted] was found to be acceptable, including a batch record review summary, and batch certificate.

The same product was also manufactured as a Special outside the control of the trial. Documentation presented included the original order, and a copy of the batch release document. Compliance with expectations for manufacture of Specials was confirmed.

C8 Production

[redacted]

Cryopreservation of cells is performed using a controlled rate freezer, with storage in vapour phase liquid nitrogen. Storage vessels are common to bone marrow, but specialist boxes are used to separate ATMPs from other materials in each dewar.

In both CBL and OBW, product mix-up risks were mitigated through temporal segregation and, for products requiring long incubation periods, spatial segregation by using different incubators for different products. The approach to campaign working were documented within [redacted] The procedure was heavily focussed on product control but gave insufficient detail of ancillary items such as BMRs.

Environmental monitoring was trended annually and the report for January 2016 to February 2017 was reviewed [redacted] The report was of an acceptable standard. At the time of inspection the particle monitor alarm was active and production was in progress. When investigated further it was found that the alarm had not been acknowledged for 90 minutes. It was therefore not possible for the operators to assess the environmental status within the area during manufacture.

There was no satisfactory environment for aseptic connection of starting materials and reagents to the [redacted]. Although this is a closed system in operation, the initial setup was performed in the Grade C room environment, without provision of localised Grade A cover for aseptic set-up, where relevant. Not all materials could be sterile welded to the equipment harness.

The CBL facility retained the capability to process viral positive donor starting material. However, deficiencies were identified with respect to the viral control measures (isolator fumigation and surface decontamination of product transferred between isolator and incubators,

C9 Quality Control

Quality Control testing takes place in various laboratories within the GOSH hospital. Following clarification many of these would be considered as 'contract laboratories', as they operate outside the control of Gene Therapy management and Quality System. QC labs were not visited during this inspection, and should be considered for future. This may be more appropriate to focus on the Gene Therapy departments control of outsourced laboratory functions.

[redacted] was used to perform endotoxin testing. The technical agreement (dated October 2015) was reviewed and was of an acceptable standard covering required activities and responsibilities.

C10 Outsourced Activities

A contract cleaning company [redacted] was responsible for the cleaning of the clean rooms. There was no technical agreement in place and there had been no assessment of the cleaners performance since 2009. Additionally, there was no evidence available that they had been trained in any local procedures, for example: [redacted] cleaning of the cleanrooms.

C11 Complaints and Product Recall

There had been no complaints o product recalls since the 2013 inspection. Deficiencies were identified in relation to the Complaints and recall [redacted]

C12 Self Inspection

Not reviewed during this inspection

C13 Distribution and shipment (including WDA activities if relevant)

There is no shipment of product under quarantine.

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

Not applicable

C15 Annexes attached

Annex **1** site risk rating

Section D List of Deficiencies

D1 Critical

None

D2 Major

2.1 There was no process simulation activity performed using microbiological growth media

Reference: EU GMP EU GMP Annex 1 (66, 67)

2.2 Cell selection of CD34+ cells by the Great Ormond Street Hospital Cell Therapies Department was not performed under a medicines manufacturing authorisation.

Reference: Human Medicines Regulations, regulation 17(1)

EU GMP Annex 2 (36d).

2.3 The control measures in place to reduce cross contamination risks from viral positive starting materials could not be verified as effective

2.3.1 With respect to the vapour phase hydrogen peroxide (VHP) fumigation of isolators:

2.3.1.1 There was no specification for the VHP gassing cycle, and no gassing cycle qualification

2.3.1.2 There was no Technical Agreement with the VHP contractor [redacted]

2.3.2 There had been no validation of viral inactivation surface treatment for bags, nor verification that sanitising agents do not penetrate the bag.

Reference: EU GMP Part 1: 1.8(ii), 7.1, 7.5, 7.7, Annex 2 (Principle, 30)

2.4 Pharmaceutical Quality systems were deficient in that:

2.4.1 [redacted] to change the supplier of human AB serum was not approved at the time of inspection although this supplier was being used.

2.4.2 Locally stored copies of change controls were seen to have additional actions added to them. There was no record to confirm that the master had been updated or that adequate oversight of these additional actions was given by the reviewers.

2.4.3 There was no deviation raised for the continued use of out of date 'old format' SOPs pending transfer to the Pharmacy/Gene Therapy integrated pharmaceutical quality system.

2.4.4 Deviations were deficient in that:

2.4.4.1 There was a lack of timely QA verification of risk to enable quality risk management prioritisation of actions

2.4.4.2 Deviation [redacted] for a starting material sterility failure had no investigation available other than in draft format available at the time of inspection. There were no CAPA and no root cause documented although the deviation was approved in February 2017.

2.4.4.3 Deviation [redacted] for a Grade A microbiological recovery was not completed in a timely manner in order to apply appropriate risk mitigating actions (raised May 2016 and approved September 2016) and had no documented root cause.

2.4.4.4 Deviation [redacted] for a sterility failure on batch [redacted] had no disposition documented; the investigation was not completed in a timely manner (5th July 2016 until 5th October 2016) and the recommendations within the investigation were not captured within the CAPA system.

2.4.4.5 Deviation [redacted] for a flood into the CBL laboratory area did not include a documented evidence that the facility was closed pending QA review of remediation work, or confirmation that no product was in the area (e.g. in incubators)

2.4.5 The complaints and recall [redacted] was deficient in that:

2.4.5.1 The contact details for the Defective Medicines reporting Centre were incorrect

2.4.5.2 There was no inclusion of the quality risk management updates to Chapter 8 (in force since 1 March 2015)

2.4.5.3 There was no consideration of impact from a reported complaint to other products

2.4.5.4 There was no reference to informing the prescribing doctor of product defects in case of unlicensed 'Specials'

Reference: EU GMP Part 1: 1.4 (xii, xiv); 1.8 (vii); 4.2; 8.9, 8.10, 8.11, 8.13, 8.15, 8.16

D3 Others

3.1 The Alarm to AHU 5 was decommissioned although it was not status labelled to identify this. The decision to decommission was not recorded within the Pharmaceutical Quality System.

Reference: EU GMP Part 1: 1.4 (xii); 3.44

3.2 Sterility assurance practices were deficient in that:

3.2.1 Holes were seen in the room ceiling air grilles to the CBL clean room.

3.2.2 The alarm to the particle monitor within the negative pressure isolator 2 had not been acknowledged for 90 minutes at the time of inspection although manufacture was taking place. It was therefore not possible for the operators to assess the environmental status within the area during manufacture.

3.2.3 The room HEPA filter integrity testing performed of the facility by [redacted] n January 2017 was not performed against any specification and was recorded 'for reference only'.

3.2.4 Papers were seen wedged between electrical boxes within the Grade C room even though the room had been recorded as cleaned numerous times.

Reference: EU GMP Part 1: 3.2; Annex 1 (1, 8, 9)

3.3 Control of contractors was deficient in that:

3.3.1 There was no documented assessment of the cleaners contracted to clean the classified areas since 2009.

3.3.2 There was no technical agreement with the cleaning company [redacted]

3.3.3 There was no documented evidence that the cleaners were trained in the local procedures, for example: [redacted] for the cleaning of the cleanrooms.

3.3.4 The technical agreement with [redacted] was not available at the time of inspection.

Reference: EU GMP Part 1: Chapter 7 Principle, 7.1, 7.4, 7.7

3.4 A sharps bin containing unknown items was seen within the office area of the OBW laboratory.

Reference: EU GMP Part 1: 5.19

3.5 The irradiation dose calculation for autologous dendritic cells failed to deliver the required dose of [redacted] There was no consideration of dose map worst case conditions, measurement error or irradiator isotope decay.

Reference: EU GMP Part 1: 1.8(i), 1.8(ii), Annex 15(3.1)

3.6 Clean room operation was deficient in that:

3.6.1 The CBL clean rooms contained unnecessary spare parts and a drywipe board. These present a challenge to cleaning, and a source of additional particulate contamination.

3.6.2 CBL clean room differential pressure between changing room (first classified area) and office (unclassified) was less than GMP guidance value of 15Pa

3.6.3 Various instructions and notices were affixed to clean room walls in both the CBL and OBW facilities with autoclave tape

3.6.4 An air ballast grille in the OBW changing room door (L4064A) was held in place with autoclave tape

3.6.5 There was no assessment of cleanroom airflows.

3.6.6 Gowning flow charts and diagrams were not reflective of text in the clean room entry SOP

3.6.7 Unofficial instructions were identified in the OBW clean rooms:

3.6.7.1 [redacted] sampling and labelling instructions were written on a 'post-it' note.

3.6.7.2 Processing centrifuge parameters were written on a whiteboard in the centrifuge room

Reference: EU GMP Part 1: 4.1, 4.2, 4.3, 5.10, Annex 1 (46, 47, 54)

3.7 There was inadequate security of product in storage

3.7.1 The liquid nitrogen tank room, used for ATMP storage, was found to be unlocked

3.7.2 Liquid nitrogen tanks were unlocked

3.7.3 Approximately 150 Great Ormond Street Hospital staff have swipe card access to controlled area, including unspecified generic card identifiers

Reference: EU GMP 1.8(ix), 3.5, 3.21,

3.8 **A new [redacted] was on the bench in the OBW office area, unlabelled as to status (e.g. in use / not in use)**

Reference: EU GMP Part 1: 5.13

D4 Comments

4.1 **The need for the following licence updates were discussed during the inspection :**

4.1.1 MIA(IMP) 17328: the following activities require authorisation for site 2091287:

- 1.5.2 (secondary packaging)

MIA(IMP) 17328: the following changes relating to contract laboratories associated with site 2091287 are required:

- Removal of laboratory [redacted]
- Addition of the [redacted] pyrogen testing laboratory

MS 17328: the following activities require authorisation for site 2091287:

- 1.3.1.1 (blood products)
- 1.3.1.2 (immunologics)
- 1.5.2 (secondary packaging)

4.2 **The inspectors have confirmed that quality control laboratories, if operated under a separate quality system to the manufacturing authorisation, should be treated as a contract laboratory.**

- GMP expectations for the management of outsourced activities (technical agreements, audits etc) will apply, and may be reviewed during future inspections of the Gene Therapy manufacturing facility.
- In the following cases, laboratories should also be named on the manufacturing authorisation, and may be subject to inspection.
    - Microbiological, biological and chemical/physical testing of finished medicinal products, i.e. final testing prior to Qualified Person certification for the purposes of batch release;
    - Stability testing of finished marketed medicinal products;
    - Environmental monitoring and or process simulation (media fill) work for sterile product manufacturer; or
    - Biological testing if it is required to be conducted in accordance with the GMP Guide as described in Annex 2 of EU GMP

4.3 **The inspectors have confirmed that there is no requirement for site 2091287 to apply for 'aseptic manufacture of large volume parenterals', on the basis of infrequent production of finished products up to 120ml. This is based upon a proportionate interpretation of the small volume parenteral guidance (100ml), and the facility's current lack of manufacturing capability for large volume products.**

4.4 Please provide the rationale for the current hand washing and gowning process applied in the CBL clean room.

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 attended by the site management and staff and the deficiencies were verbally accepted.

F2 Assessment of response(s) to inspection report

A response was received on 18 August 2017. Several requests for further information were required, as the responses indicated a lack of investigation (with appropriate CAPA relevant to causal factors), and included significant time periods to implement remediation. Concerns regarding available resources to implement corrective action were raised with senior management.

F3 Documents or Samples taken

None

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

The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
Directive 2001/83/EC, Directive(s) 2003/94/EC and 2011/62/EU	✓
GMP as required by HMR 2012 (as amended)	
Directive 2001/20/EC	✓

Directive 2001/82/EC	
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	

and is acceptable for the products in question.

Name and Dated Signature of Inspector (s):

[redacted]

Dated: 9/10/17

Dated: 11/10/17

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	4	Last inspection:	0
Other deficiencies this inspection:	8	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 (does not require counter-signature for RR II)
	Other discriminatory factor (record details and justify below)

(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 I, II, III):

[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