Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Great Ormond Street Hospital for Children NHS FT
Zayed Centre for Research into Rare Disease in Children (ZCR)
20 Guildford Street
London
WC1N 1DZ

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Inspection, Enforcement & Standards Division, MHRA
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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection of ZCR after initial site approval in 2022 and addition of further activities via Variation.

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

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

Details of Product(s)/ Clinical trials/Studies: Cell and Gene Therapies as ATMPs

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	Y
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: *Specials, IMP activities*	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 16th May 2023: remote IMP importation oversight review
24-25th May 2023: on site

Lead Inspector: [redacted]

Accompanying Inspector(s): Not applicable

Case Folder References: Insp IMP 17328/23930512-005

Section B General Introduction

B1 Background information

The newly built Zayed Centre for Research into Rare Disease in Children GMP Facility (ZCR-GMP), located at 20 Guildford Street was approved following inspection in 2022. Subsequent to this a variation was submitted to add IMP Importation oversight and manufacture of Viral Vectors.

Viral Vector work was to be undertaken by [redacted] a Non-GOSH GMP Organisations (NGGO) operating under the GOSH licence. These were intended viral vectors for incurable disorders such as [redacted]

Previous Inspection Date(s): 16 – 19 August 2022

Previous Inspectors: [redacted]

B2 Inspected Areas

IMP Importation oversight

Manufacture and release of Viral Vectors.

Control of Specials / Unlicenced products

Limitations / exclusions to inspected areas

Any general inspection topics, as assessed via the initial site inspection August 2022

B3 Key Personnel met/contacted during the inspection

Name	Position
[redacted]	

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted] (18/05/23)	Y
Compliance Report	22 May 2023	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 GOSH ATMP Head of Quality and QP retired, [redacted] Quality department restructured with [redacted] at the current time.

Additional posts of Production Manager and Service Manager recruited.

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

The site was in the process of [redacted] on the licence for ATMPs.

C2 Action taken since the last inspection

Not all actions were assessed during this inspection. However, the site notified via an Interim compliance report in April 2023 (beyond action due dates) that there were delays to completion timelines. All actions were due to be completed by summer 2023, with a commitment "that no clinical manufacturing activities will be scheduled until most of inspection CAPAs closed by end of May 2023".

C3 Starting Materials

General

The supply of Plasmid was not controlled, with no item code or specification in place.

Where no material specifications were in place, [redacted] was ongoing to manage this. All materials were currently released against CofAs approved by QA. This CAPA was not robust. A deficiency was raised for Component and Material controls, see Section D3.

Compliance with TSE Guidelines

Not assessed during this inspection.

API Compliance

Not applicable for Viral Vectors

C4 Pharmaceutical Quality System

An established quality system was in place and had been previously inspected, as the site already held an MIA(IMP) and MS licence.

Procedures relating to the core aspects of the quality system were not reviewed in detail unless specific changes had been required with respect to the implementation of the IMP import oversight process or introduction of viral vector processes.

Oversight process

A change control [redacted] was raised on 23rd March 2022 for the implementation of the oversight process, and this remained open. Note: The site already held an MA(IMP) that allowed importation.

Change control [redacted] was supported by change control [redacted] raised on 24 Feb 2022 for an emergency import, which was discussed with the MHRA at the time. This was raised for the urgent supply for one specific patient. The CC was closed in March 2022. Documentation raised for this supply were then superseded/updated for the future supplies.

Actions beyond "raising QP Oversight of Imported IMPs SOP" were not clearly defined. A detailed gap analysis against the MHRA published guidance had not been conducted as part of the change control.

Procedure [redacted] restated the issued MHRA guidance. This did not provide any detail on how this was to be implemented at GOSH. For example, the SOP restated that the oversight QP must verify that the PQS includes "Management of Product Specification Files (not all detail in the PSF will be required, but relevant information should be available and maintained up to date". Yet no detail or instruction was given as to what was required, although the form did include a small list. The SOP did not document how tasks could be delegated or documented if delegated.

The SOP referred to the form [redacted] to record oversight activities. The form referred to evidence of QP Batch certification via Access to the certifying MIA(IMP) holder's internal systems (e.g. a global ERP) – which would not be applicable to GOSH.

The procedure and form did not clarify whether importation oversight was for shipments into GOSH or whether this was also to support shipments direct to sites (which required additional information). There was no process to assess the physical shipment controls or the temperature assessments prior to release of each shipment of imported IMPs received into the UK, beyond a review of any excursion.

The entire process was for a batch and did not include details on individual shipment information and as such the assessment of each shipment. The final assessment was regarding whether the batch could be made "available for use in GB clinical trial sites".

There was no information on where relevant documents were held or what revision of documents were assessed. The SOP only included information on where to store the completed form.

A register was used [redacted] to record oversight activities.

The records for the emergency importation oversight [redacted] as above) were reviewed and acceptable for the process in place at the time. (This was a 2-8□c product with a 42-hour shelf life from filling). Product was shipped under quarantine, where final EU QP certification processes included assessment of temperatures during shipment to GOSH.

Viral vectors

The Change Control [redacted] for the Introduction of the [redacted] manufacturing was reviewed, this was a high-level document.

The [redacted] was reviewed, this was in "draft approved" status with the intention to make this live once the licence variation was approved. There was no requirement to set up the Product Specification File (PSF) prior to batch review and controls were lacking with regards to differences of intended material designation. The intended approach of a single PSF with multiple appendices for different vectors would not allow a robust approach.

A deficiency was raised for Viral vector manufacturing ordering and Release processes, see Section D3.

Investigational (IMP) and Unlicenced products

This was assessed as part of the review of the [redacted]

This did not include appropriate instructions or controls for the labelling and release of Specials under the MS licence. Records for Specials batch [redacted] were reviewed. A Major deficiency was raised, see Section D2.

For IMPs, the SOP focused on labels provided by Sponsors, the level of information and stated requirements were not sufficient or correct. A new change control had been opened to look at how to generate labels in house, and a new SOP, this did not have any action to review or update the Labelling SOP reviewed.

C5 Personnel

The SOP [redacted] for Oversight of Imported IMPs was only applicable to the QPs named on the licence, however this did not take into account any staff who may be involved within QA due to delegated activities. QA Training was intended to be covered by the issuance of [redacted] which was a specific QA training module ready for issuance on approval of the licence variation.

The Quality Agreement in place for the QP contracted for GOSH [redacted] was reviewed and considered acceptable.

Training records for [redacted] Manufacturing Scientist [redacted] were reviewed. This showed significant system failings and a deficiency was raised, see Section D2.

C6 Premises and Equipment

All filters for TFF processes were single use. Pressure tests for commercial filters were carried out the day prior to production with dry filters and this was not justified.

The production of viral vectors occurred in the 2 assigned rooms within the ZCR facility.

C7 Documentation

[redacted] SOPs and documents were held within the ZCR Quality system with a prefix of [redacted] these were password protected where required to retain confidentiality in the event of further NGGOs being onboarded. All documents included approval from the ZCR quality team.

Hard copy documents did not include appropriate footers to reflect date printed or expiry of the printed copy.

Multiple documents were specific to [redacted] yet were generic topic SOPs on the use of standard equipment such as operation of the Bio-Welder and balances. It was not clear why these were not ZCR SOPs.

C8 Production

No manufacturing for patient supply had commenced from the ZCR facility.

Production processes involved open manipulation with via Tri clover connections within the Isolators, and not quick fit or aseptic connections.

Process Qualification: the following associated documents were reviewed:

[redacted]

The [redacted] was reviewed. This did not provide sufficient detail to ensure that the process was repeatable or consistent following the same approach, handling methods and manipulations.

The change control for the introduction of viral vectors [redacted] had not considered the transfer of materials required for this process or the potential for leachable impact. The Risk assessment [redacted] was reviewed, this did assess material type and included manual transfer with an inclusion of a sporicidal step. However, there was no comparison of this to the existing GOSH ZCR processes, procedures or manual transfer qualification activities, to determine suitability.

The CC31 for process changes had taken into account the cumulative effect of multiple changes and was due to be supported by a further PV run.

Any spent / waste viral vector was decontaminated via the addition of a [redacted] solution. Solutions were held overnight prior to disposal.

An Aseptic process simulation (APS) Viral vector run was observed in room 2, during the stages to mimic the Day 5 Transfection process, following [redacted].

Major deficiencies were raised for Viral Vector Validation controls and also Viral vector Production and aseptic controls, refer to Section D3.

C9 Quality Control

Not assessed during this inspection.

C10 Outsourced Activities

The technical Agreement with [redacted] related to Importation oversight was reviewed. This was in place from February 2022 specifically for the single emergency shipment covered by [redacted] (see above in C4) and was no longer valid.

This QTA document did not cover the responsibilities of Import oversight appropriately, with details included such as finance / insurance for the trial itself. Whilst deemed appropriate for the single shipment this covered it would not be applicable to future trials where GOSH was carrying out importation oversight. No appropriate template or master QTA was available.

C11 Complaints and Product Recall

Not assessed during this inspection.

C12 Self Inspection

Not assessed during this inspection.

C13 Distribution and shipment (including WDA activities if relevant)

Viral vectors manufactured at ZCR for use in the Royal Free were intended to be shipped across in cryoshippers for the short transit.

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

1 CRITICAL

None

2 MAJOR

2.1 **Viral Vector (VV) Validation controls were deficient in that:**

2.1.1 Aseptic process simulation (APS) controls were lacking in that:

2.1.1.1 Protocols did not ensure that the actual worst-case scenarios were formally defined and assessed, including (but not exhaustively) those such as glove changes across different stages, the number of openings of flasks and the number and types of transfers in the Grade A isolator.

2.1.1.2 The [redacted] lists process steps as interventions and did not manage actual expected interventions or potential frequency.

2.1.1.3 APS Batch Manufacturing Record instructions did not ensure that processes mimicked the handling of multiple sets of flasks with regards to transfer into the isolator, that flasks were appropriately handled to ensure that all surfaces were coated in media nor that records were made of the interventions carried out during the process.

2.1.2 There was no formal assessment of components and equipment introduced into the Grade A isolator to ensure that manual sanitisation processes were captured within the scope of existing qualification activities.

2.1.3 Process Validation (PV) controls were deficient in that:

2.1.3.1 [redacted] did not justify why a single PV run was acceptable.

2.1.3.2 PV protocols did not justify the requirement to add [redacted] of [redacted] with regards to any criticality of the volume, given that additions were made against rough marker pen lines on a T175 flask via manual pouring.

2.1.3.3 PV batch record [redacted] was processed with the omission of VHP cycles at all required stages and the use of manual sanitisation without any explanation or justification, and there was no explanation for why no finger dab samples had been taken for the second set of EM plates for the Day 5 processing.

2.1.3.3.1 The lack of VHP cycles was not assessed or defined with respect to the impact to the isolator or any components that may have been included in the VHP cycle.

2.1.3.3.2 The Isolator Set-up form [redacted] had not been updated to confirm when a manual process may be substituted for a VHP cycle and what checks were required, following site assessment.

2.1.3.4 The [redacted] was deficient in that:

2.1.3.4.1 There was no summary of the actual worst-case parameters or frequency of interventions that were completed.

2.1.3.4.2 There was no risk assessment or formal review of all deviations associated with the PQ batch and processes.

2.1.3.4.3 This did not actively include a summary or conclusion statement, to confirm that the PQ had not been successful.

2.1.3.4.4 [redacted] related to updates to the process controls and documentation prior to the [redacted] run was not completed in a timely manner and did not ensure that this was fully approved prior to [redacted] being carried out.

2.1.3.4.5 The interim report for [redacted] did not ensure that master documentation was made inactive despite a comment that these must be updated prior to any future clinical run.

Reference: EU GMP A1.22, A1.24, A1.67, A1.68, A1.82, A15.2.7, A15.3.1, A15.5.7, A15.5.9, A15.5.10, A15.11.4

2.2 **Viral vector (VV) Production and aseptic controls were deficient in that:**

2.2.1 Batch records did not include appropriate detail to ensure a consistent approach to the management of materials or stages as evidenced by:

2.2.1.1 There were no instructions to ensure a consistent process for handling multiple sets of flasks during production.

2.2.1.2 There was no requirement to record the item numbers or define the format or volume of supplied Plasmids.

2.2.2 The management of materials and conditions within the Grade A isolator were deficient in that:

2.2.2.1 There was no control to ensure that air flow patterns were not impacted by multiple items being placed over extract vents on the base of the isolator.

2.2.2.2 A pipette stored below the level of the base of the isolator, on a small ledge next to the front face, was used for sampling during the APS process.

2.2.2.3 Marker pens used in the Grade A isolator for Viral vector processing were not sterile.

2.2.3 There was no requirement to clearly identify flasks with the stage of manufacture during Aseptic Process simulation runs. It was noted that flasks were incorrectly placed back into the hatch for transfer out of the isolator during the APS in error.

2.2.4 Material and component transfer processes were deficient that:

2.2.4.1 Sanitisation spray of components into the transfer hatch such as pipettes was deficient in that this did not ensure that all surfaces were sanitised.

2.2.4.2 It was not possible to ensure that appropriate sanitisation of all surfaces of support equipment such as racks for 2ml vials and 50ml tubes, as these were not fit for purpose with respect to design.

2.2.4.3 No review of equipment or component presentation and transfer had been carried out to ensure reduced contamination risk to the Grade A environment as evidenced by:

2.2.4.3.1 Multiple Singe pipettes being transferred into the isolator via spray versus the use of an irradiated bag of multiple units.

2.2.4.3.2 Filter assembly equipment supplied in overly large plastic bags, resulting in hard to manually handle during spraying processes, and no consideration of use of multiple layers of bags to aid in the transfer process via the potential to eliminate the need for spraying.

Reference: EU GMP C3.34, C3.36, C4.4, C4.17(c), C4.18(d), C4.20(d), C5.10, C5.12, A1.21, A1.22, A1.24, A1.81

2.3 **Specials release and Labelling controls were deficient in that:**

2.3.1 Labels for MS did not comply with MS guidance and BP requirements (e.g., no inclusion of MS licence number and inclusion of “for Clinical Use”) and the associated SOP incorrectly included references to Annex 13 (IMP) requirements.

2.3.2 Specials batch [redacted] was released without an appropriate label, the release certification and associated checklist did not provide justification and did not reference the deviation that had been raised to address the identified failures in the Specials controls.

2.3.3 [redacted] related to a review of Specials management had not been formally investigated despite being raised on 11/Feb/23 and no actions had been raised.

Reference: MHRA Guidance for 'Specials' Manufacturers
https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

British Pharmacopoeia: Supplementary Chapter V Unlicensed Medicines and the General Monograph on Unlicenced Medicines

2.4 **Training was deficient in that:**

2.4.1 There was no requirement for GMP induction training.

2.4.2 Training records did not distinguish start date with NGGOs versus commencement of involvement with operations under GOSH licences, as such it could not be determined if applicable training was completed prior to the commencement of activities within the GMP facility.

2.4.3 There was no process in place to track SOP training to ensure that staff were trained in latest versions of SOPs.

2.4.3.1 Training records for [redacted] showed multiple SOPs overdue for more than 6 weeks.

2.4.4 Training module template forms introduced in February 2023 were still not in use for personnel to provide evidence of training and competency.

2.4.4.1 Forms for [redacted] were completed for SOP awareness only on 25/5/2023 follow the request for records and no training competency was included, when [redacted] observed carrying out APS runs.

Reference: EU GMP Chapter 2 Principle, C2.9(v), C2.11, C4.29

3 OTHERS

3.1 **Component and Material controls were deficient in that:**

3.1.1 There was no process to ensure that Material Specifications were required nor in place.

3.1.1.1 This was a repeat finding from the August 2022 inspection (Ref # 2.3.5.6.1 and 3.3.3)

3.1.1.2 Controls via a new [redacted] raised relating to Material specifications following a client audit in February 2023 were deficient in that:

3.1.1.2.1 All actions had been assigned a due date of end June 2023 for updating the Material receipt SOP, creating a specification template, and generating all required specifications. However, the site agreed during inspection that this was not achievable with regards to specification generation.

3.1.1.2.2 No action had been raised to define the requirement for material specifications nor confirm their requirement for new materials or components.

Reference: EU GMP C1.5, C4.13, C4.14

3.2 **Viral vector manufacturing ordering and Release processes were deficient in that:**

3.2.1 There was no SOP in place to describe the full requirements to set up a new manufacturing vector request or manufacturing order.

3.2.2 Batch records were only required to be retained for a minimum of 5 years, without any consideration of the intended use of the material.

3.2.3 Release processes did not detail the different requirements for documentation and checks for VV produced as starting vs active vs final products, nor the difference with respect to release certification documentation.

3.2.4 Release checks did not detail the requirements to check all the aspects of the Product Specification File (PSF) were applicable for VV IMPs.

3.2.5 There was insufficient detail on the inclusion of VV work onto the GOSH QP register, to ensure that these consistently recorded the level and type of activity undertaken / product released.

Reference: EU GMP C1.2, C1.4(xv), C4.11, C5.63, C5.64, Chapter 6 Principle, A13.9, A13.38, A16.1.6(iii)

3.3 **Controls for IMP importation oversight controls were deficient in that:**

3.3.1 The Oversight checklist and release statement was focussed on batch assessments and did not include appropriate details on individual shipment information and as such the release of each shipment.

3.3.2 There was no process in place to ensure products shipped to external sites would not be administered prior to an assessment of the physical shipment controls or the temperature. The SOP and checklists were not clear on the scope of Importation oversight or additional requirements linked to shipments to external sites.

3.3.3 There was no template QTA in place with sponsors to manage the importation oversight responsibilities.

Reference: EU GMP C1.4(xv), C7.1, C7.14

3.4 **Documentation controls and records were deficient in that:**

3.4.1 Hard copy printed SOPs were not controlled to ensure that these were current, as the footnote included the comment that the copy "would expire upon issue of the next revision".

3.4.2 Batch records were not completed contemporaneously as evidenced by steps not being completed / signed for prior to subsequent steps.

Reference: EU GMP C4.1, C4.2, C4.8

4 COMMENTS

4.1 The site is reminded that they must notify the MHRA inspectorate if they are not able to fulfil inspection commitments via an interim compliance report in advance of missing deadlines.

4.1.1 Actions from the August 2022 MHRA inspection were overdue and only notified to the inspectors via site risk assessment documentation several months beyond the due date.

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 company accepted the deficiencies highlighted at the closing meeting.

F2 Assessment of response(s) to inspection report

A response was received 2nd July 2023 which was not considered satisfactory. Additional clarification for several points was requested from the company on 16th August 2023 and further responses were received on 25th August 2023 which was deemed to be satisfactory.

F3 Documents or Samples taken

None retained

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
GMP as required by the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	✓
The Medicines for Human Use (Clinical Trials) Regulations 2004	✓
Regulation 5 of the current Veterinary Medicines Regulations	
Regulation C17 of the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 13th October 2023

Accompanying Inspector: N/a **Date:**

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	4	Last inspection:	4
Other deficiencies this inspection:	4	Last Inspection:	6

(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

This was not a full scope inspection following the initial inspection of the ZCR facility in Aug 2022

(e). Risk Rating Result Incorporating Discriminatory factors (✓ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

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

[redacted]

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

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments (Risk rating level 0, I, II):

Expert / Operations Manager / CMT (delete as appropriate)
Risk Rating:
Comments: None
Name: Date:

(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