Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

# INSPECTION REPORT

## Celerion GB

## 22-24 Lisburn Road
## Belfast
## BT9 6AD

**Head Office:**
**Inspection, Enforcement & Standards Division, MHRA**
**151 Buckingham Palace Road**
**London SW1W 9SZ**

Telephone: 020 3080 6000
Email: info@mhra.gsi.gov.uk

## Section A Inspection Report Summary

**Inspection requested by:** MHRA

**Scope of Inspection:** Routine Re-Inspection

**Licence or Reference Number:** MIA(IMP) 15059

**Licence Holder/Applicant:** Celerion GB

Section 40 & 43

**Details of Product(s)/ Clinical trials/Studies:** Celerion are an early [redacted] clinical trials unit with expertise in respiratory studies.

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

*Aseptic processing is restricted to preparatory manipulations for already sterile products

**Name and Address of site(s) inspected (if different to cover):**
**Site Contact:** [redacted]

**Date(s) of Inspection:** 21st June 2016

**Lead Inspector:** [redacted]

**Accompanying Inspector(s):** N/A

**Case Folder References:** GMP/IMP 15059/27971/-0013

## Section B General Introduction

### B1 Background information

Celerion is a provider of innovative early clinical research solutions. The focus of the company is to provide comprehensive clinical research services to the pharmaceutical and biotechnology community. Celerion has a global presence with representation in USA, Canada, Germany, Austria, Switzerland, Singapore, South Korea and the UK, which offer a complete suite of early clinical services. In January 2016, Assign Clinical Research joined Celerion as part of a strategic acquisition to expand Celerion's capabilities in conducting early clinical research studies in patients.

Celerion GB has had a strong presence in Belfast for over 20 years and is located in a historic building that was first opened in 1874 as the Samaritan Hospital. The Belfast unit specialises in Phase I/IIa with expertise in respiratory studies. All manufacturing activities are performed in the two pharmacies and the adjoining biologicals containment facility, which are located in the Samaritan building.

Sectio n 40

**Previous Inspection Date(s):** 10 – 11th June 2013

**Previous Inspectors:** [redacted]

### B2 Inspected Areas

Introductory meeting
Review of compliance report to identify current activities and future planned changes
Review of responses to deficiencies from the last inspection
PQS and records associated with manufacture, packaging storage and control of IMPs
Tour of GMP facilities
Batch certification process
Closing Meeting.

**Limitations / exclusions to inspected areas**

There was no production activity in progress during the inspection

Training records, self-inspection programme and procedures for complaints and recalls were not reviewed in detail during this inspection.

### B3 Key Personnel met/contacted during the inspection

[redacted]

Section 40

[redacted]

**B4 Documents submitted prior to the inspection**

| Document | Version /Date of document | Reflected activities on site? |
|---|---|---|
| Site Master File | 2016-02 | Y |
| Compliance Report | 3rd May 2016 | Y |
| Comments:<br>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 relevant

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

None planned

**C2 Action taken since the last inspection**

The previous inspection identified one major deficiency relating to change control and four other deficiencies related to deviation reporting, training, personnel, and vendor management. The company appeared to have adequately addressed the deficiencies from the last inspection, however the biological containment suite has not been used since the last inspection. An appropriate requalification plan and associated change control will need to be implemented before the suite is utilised for GMP manufacture.

Section 43

## C3 Starting Materials

Responsibilities for sourcing and supply of starting materials including API compliance and TSE considerations are agreed with the [redacted] and documented in pharmacy technical agreements. Starting material delivery and usage records are retained in study specific pharmacy files. Support documentation including certificates of analysis, TSE certificates, and QP release statement for manufactured products are expected for each batch of starting material including for product contact packaging materials.

## C4 Pharmaceutical Quality System (PQS)

The quality management system (QMS) is based on global policies and procedures and is supplemented by local procedures where appropriate. Deviations, quality incidents, CAPA, and pharmacy change control are documented using an eform and managed through the Sharepoint system. Deviation, quality incident and CAPA metrics are reported to the bi-monthly Quality Review meeting and broader issues are discussed at the quarterly global Quality Council meeting. Such meetings do however have more of a GCP focus and the QP is not routinely involved. Although the QP appeared to be aware of new or revised regulatory requirements that would impact GMP, such changes are not routinely discussed at the Quality Review/Quality Council meetings, and there was a lack of evidence to show that any changes identified had been implemented in site procedures. Examples of completed change controls ([redacted] completed deviations [redacted] were reviewed. There was evidence to confirm that the [redacted] had evolved since the last inspection, however the need for further improvement was identified. See Section D.

## C5 Personnel

Satisfactory numbers of personnel were in place for the activities undertaken and licence held. Personnel met were experienced and competent in their approach. Training involves a combination of SOP, practical based and periodic GMP/GCP training according to a job specific training programme. Training is logged in [redacted] which is an [redacted] based system that provides email notifications to alert staff to SOP updates. Staff involved in GMP activity are required to complete annual GMP refresher training which is delivered by the QP. Training records were not reviewed in detail as evidence of training, CV and job description for the Clinical Research Pharmacist-In-Charge and the Senior QA Auditor had previously been reviewed to support naming them as key personnel on MIA(IMP) 15059.

## C6 Premises and Equipment

All manufacturing activities are performed in the two pharmacies and the adjoining biologicals containment facility, which are located on the 3rd floor of the Samaritan building. Entry is restricted using a cryptag system. Stand-alone air-conditioning units are used to control temperature within the pharmacies and an electronic system is used to monitor the temperature and includes an audible alarm, email, and text message alert service.

One of the pharmacy rooms contains a [redacted] biological safety cabinet which is used for aseptic processing e.g. reconstitution and dilution of already sterile products. A separate HEPA filtered HVAC system supplies air to the biologicals containment facility. The biological containment suite has not been used since the last inspection. An appropriate requalification plan and associated change control will need to be implemented before the suite is utilised for GMP manufacture.

Section 43

## C7 Documentation

The QP batch certification process [redacted] was reviewed as part of the inspection and was found to be broadly sound and comprehensive. The QP uses a QP release checklist and has access to the pharmacy file to confirm all the necessary criteria are met. The pharmacy files for study numbers [redacted] were reviewed and found to be comprehensive. The technical agreements in place with [redacted] were comprehensive. Study number [redacted] involved Celerion being responsible for the importation of IMP, and included evidence of a third party audit of the manufacturer and assessment of auditor qualifications to support the QP declaration for importation from a third country.

Underlying systems and processes for generating, checking and control of documentation appeared satisfactory. There was evidence to confirm that the content of SOPs and [redacted] records had evolved since the last inspection.

## C8 Production

There was no production activity in progress during the inspection, although the isolator in [redacted] had been is use earlier in the day. A cleaning wipe was present inside the isolator despite the isolator being identified as clean in the cleaning log entry for 21st June 2016. See Section D.

Study specific materials are stored within designated cupboards in the pharmacy rooms. A separate storage cupboard is available to segregate quarantined or rejected stock. A shelf space layout diagram/map is used to identify the location of study specific materials stored in the refrigerator, to reduce the time the door is opened to retrieve the required items.

Manufacturing operations are generally limited to simple weighing, mixing, dilution, packaging and labelling, which are either done at the pharmacy bench or using the isolator. All product contact items are either disposable or dedicated to a specific study to prevent cross-contamination. An electronic system ([redacted] has been implemented to track and record the calibration and maintenance requirements for multi- use equipment.

## C9 Quality Control

No QC testing is undertaken at the site.

## C10 Outsourced Activities

Testing of starting materials is contracted out to [redacted] and environmental monitoring is contracted out to [redacted] and [redacted] The site has two contract QPs named on the licence, who are utilised on an ad-hoc and infrequent basis. The company's policy with respect to refresher training of contract QPs to ensure current knowledge of [redacted] and study specific requirements, prior to them certifying product was not documented in [redacted] See Section D.

## C11 Complaints and Product Recall

Procedures for complaints and recalls are in place but were not reviewed during this inspection.

## C12 Self Inspection

The self inspection programme is managed globally by QA and covers both GMP and GCP aspects. A study audit is conducted for each clinical study which includes pharmacy/IMP activities and an annual programme of system and process related audits are in place across all Celerion sites. Audit findings and close out of CAPA plans are discussed at the quarterly global

Quality Council meetings. The scope of individual audits and details of any deficiencies identified were not reviewed during this inspection.

**C13 Distribution and shipment (including WDA activities if relevant)**

Not applicable, trial materials are for in-house use only.

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

None

**C15 Annexes attached**

Annex 1 site risk rating

## Section D List of Deficiencies

**D1 Critical**

None

**D2 Major**

None

**D3 Others**

3.1 The change control procedure was deficient in that there was a lack of detail documented in the change control report to confirm how actions had been assessed as complete. Where the report covered more than one action, there was no documented acknowledgement that some actions had already been completed.

***Reference: EU GMP Chapter 1, 1.4(xii, xiii), Annex 15, 44***

3.2 The process in place for the management of contract QP services was not documented to ensure contract QPs would receive appropriate training in company and study specific procedures prior to performing any QP certification activities.

***Reference: EU GMP Chapter 1, 1.4(vii), Chapter 7, 7.5, 7.7***

3.3 Operational practice was deficient in that a cleaning wipe was present inside the isolator despite the isolator being identified as clean in the cleaning log entry for 21st June 2016.

***Reference: EU GMP Chapter 5, 5.18, 5.21 organisational measures (vii)***

3.4 The pharmaceutical quality system was deficient in that there was no formal process to demonstrate that the impact of regulatory changes had been assessed and implemented in site procedures. Although an ad-hoc system of review was being practiced by the QP, there was no evidence to confirm that the batch certification SOP had been reviewed in light of changes to Annex 16, or that toxicological considerations had been included as part of the risk management process for new product introduction following updates to Chapters 3 & 5 requirements.

***Reference: EU GMP Chapter 1, 1.4(iii), 1.8***

**D4 Comments**

None

## Section E Site Oversight Mechanism

| Site referred or to be monitored by: | Tick (✓) | Referral date | Summary of basis for action |
|---|---|---|---|
| Risk Based Inspection Programme | √ | | |
| Compliance Management Team | | | |
| Inspection Action Group | | | |

## Section F Summary and Evaluation

**F1 Closing Meeting**

A post inspection meeting was attended by key personnel listed in B3 during which the company verbally accepted the deficiencies identified and indicated that they would respond positively to the issues raised.

**F2 Assessment of response(s) to inspection report**

A satisfactory response was received from the company on 21st July 2016.

**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 | N/A no licensed products |
| GMP as required by HMR 2012 (as amended) | N/A no "Specials" products |
| Directive 2001/20/EC | √ |

| | |
|---|---|
| Directive 2001/82/EC | N/A no Vet products |
| Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU | N/A no distribution activity |

and is acceptable for the products in question.

**Name and Dated Signature of Inspector (s):**

Section 40

**Signed:** [redacted]

Name [redacted]

**Dated:** 26th July 2016

**Annex 1**

**GMP Site Risk Rating**

**(a). Inspection Findings**

| | | | |
|---|---|---|---|
| Critical deficiencies this inspection: | 0 | Last inspection: | 0 |
| Major deficiencies this inspection: | 0 | Last inspection: | 1 |
| Other deficiencies this inspection: | 4 | Last Inspection: | 4 |

**(b). Provisional Rating based on Inspection Output** (✓ applicable box)

Section 43

| 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) |

Section 43

(d). Inspectors Comments Related to Discriminatory Factors

[redacted]

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

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

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

[redacted]

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

[redacted]

(h). Conclusions

[redacted]

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

[redacted]

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

Section 43

| 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