INSPECTION REPORT

Celerion,
22 – 24 Lisburn Road
Belfast
BT9 6AD
Northern Ireland.

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SECTION A INSPECTION REPORT SUMMARY

Inspection requested by: MHRA

Scope of Inspection: Routine re-Inspection to assess compliance with EU GMP and Medicines for Human Use (Clinical Trials) Regulation 2004 and to assess variation MIA(IMP) 15059-M-0019 to add additional activities and change of key personnel.

Licence or Reference Number: MIA(IMP) 15059

Licence Holder/Applicant: Celerion GB Limited

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Details of Product(s)/ Clinical trials/Studies: Celerion are a [redacted] accredited unit who run healthy volunteer clinical trials.

Activities carried out by company:

	Y/N
Manufacture of Active Ingredients	N
Manufacture of Finished Medicinal Products	Y
Manufacture of Intermediate or Bulk	N
Packaging	Y
Importing	Y
Laboratory Testing	N
Batch Certification and Batch Release	Y

Name and Address of site(s) inspected:
Celerion,
22 – 24 Lisburn Road
Belfast
BT9 6AD
Northern Ireland

[redacted]

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

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

References: GMP IMP 15059/27971-0011

Final Conclusion/Recommendation: The site is generally compliant with EU GMP and the Medicines for Human Use (Clinical Trials) Regulation 2004. A Type 1 letter was sent and after further requests for additional validation information, a satisfactory response received. The current licence can continue to be supported. Variation MIA(IMP)15059-M-0019 to name [redacted] as Person Responsible for QC and to add biological manufacture can be supported.

Name and Dated Signature of Lead Inspector:

[redacted]

Signed: [redacted] **Dated:** 18th February 2014

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 four clinical facilities located in Belfast, Nebraska, New Jersey and Arizona. Celerion 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.

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The Belfast unit has a 78 bed clinical unit specialising in [redacted] with expertise in respiratory studies. All manufacturing activities are performed in the two pharmacies located in the Samaritan building. The newly installed Biologicals containment facility is located between the pharmacy and pharmacy office.

Previous Inspection Date(s):
3rd February 2011

Previous Inspectors:
[redacted]

B2 Inspected Areas

Below is an outline of areas covered during the inspection:

- Introductory meeting
- Review of compliance report to identify current activities and future planned changes
- Review of responses to deficiencies from the last inspection
- Quality system and records associated with packaging, storage and control of IMP
- Validation package for newly installed Biologicals Containment facility in relation to variation MIA(IMP) 15059-M-0019
- Job description and training records for Responsible Person for QC in relation to variation MIA(IMP) 15059-M-0019
- Batch certification
- Closing meeting

B3 Key Personnel met/contacted during the inspection

[redacted]

B4 Documents submitted prior to the inspection

GMP compliance report dated 16th May 2013
Site Master File version - 2013

SECTION C INSPECTOR'S FINDINGS

C1 Summary of significant changes

Changes since Previous Inspection

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Personnel – [redacted] replaced [redacted] as Pharmacy Technician. [redacted] replaced [redacted] as site QA lead.

Facilities – biological containment room installed and associated procedure written.

Procedures – Importation of IMP and Pharmacy Change Control procedures added to quality system.

Future Planned Changes

No significant changes are anticipated at this time.

C2 Action taken since the last inspection

The company have adequately addressed the deficiencies from the last inspection.

C3 Assessment of the Site Master File

An electronic version of the Site Master File (SMF) was reviewed in preparation for the inspection. The SMF mainly comprises a copy of the MIA(IMP) and site floor plan drawings. There is limited production and quality management system information but cross-reference to associated procedures are included. The site floor plans have been updated to include the location of the biological containment room, however no further information about the construction or operation of the facility is included in the text of the SMF.

C4 Starting Materials

Responsibilities for sourcing and supply of starting materials is agreed with the [redacted] and documented in pharmacy technical agreements. Starting material delivery and usage records are retained in study specific pharmacy files.

C5 Quality Management

The quality management system (QMS) is based on global policies and procedures and is supplemented by local procedures where appropriate. GMP related changes to premises, equipment, and materials are controlled by [redacted] Pharmacy Change Control. The newly implemented procedure included basic change control considerations, but did not contain sufficient control points to ensure any changes were implemented safely. (Refer to deficiencies section of the report). Deviations are managed using a two tiered process. Quality Incidents described in [redacted] do not include all non-conformities. Quality incident investigations and CAPA are only raised when a problem that affects the quality of data or service provided and for which CAPA is appropriate. Most non-conformities are therefore managed as deviations [redacted] however a quality incident is raised is the non-conformity is identified as

a recurring issue or considered high risk to business. Deviations are logged and tracked using an electronic system that is used to provide metric. The control of deviation reporting was deficient in terms of the timeliness of reporting, close-out of investigations, and a lack of detail documented in the investigation report. (Refer to deficiencies section of the report).

Key site personnel are involved in weekly quality meeting to discuss any operational quality issues. In addition, there is a two weekly quality incident review team meeting and monthly QA meeting at site. It was stated that [redacted], the proposed person to be named as Quality Controller on the licence was not actively involved in day-to-day site operations or quality meetings. His interactions with the site appeared to be limited to a quarterly global Quality Council meeting.

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C6 Personnel

GMP related activities are performed by dedicated staff with access to the Pharmacy and labelling functions restricted to these personnel. 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. CV, job description and training records for the Clinical Trials Pharmacist, Pharmacy Technician and the proposed Responsible Person for QC were reviewed. The new technician had a comprehensive training record detailing all of the SOPs that had been read. It was noted that there was no system to ensure that personnel had completed the requisite training prior to performing a function. There was a lack of evidence of QC and EU GMP experience documented to support naming [redacted] as Quality Controller. (Refer to deficiencies section of the report).

C7 Premises and Equipment

The site has an isolator located in a non-classified area but there were no limits given for the type of aseptic process that would be allowed. A comment was made that the licence and the GMP certificate would need to either have the aseptic function removed or that they would both need to have detailed restrictions with regards to aseptic processing. The company were asked to provide suggested wording for this restriction comment.

The new biological containment suite was reviewed in depth; there were a number of deficiencies raised as a major deficiency regarding the control of the change and the qualification of the suite. (Refer to deficiencies section of the report).

The company has access to in house statisticians, functions such as randomisation and analysis of data can be performed in house or by the client. Break codes are kept at the facility.

C8 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 with references to the [redacted] and [redacted] including any amendments and conditions. The technical agreements in place with [redacted] were comprehensive.

The vendor management process [redacted] was reviewed. The service providers on site at Celerion were excluded from the vendor audit programs on the basis that records of calibration/service/maintenance are reviewed during pharmacy system audits. This approach

had failed to ensure contractors were aware of the GMP related requirements and standards of work expected (refer to deficiencies section of the report).

C9 Production

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The packaging of period [redacted] for study [redacted] was witnessed. This involved the packing of [redacted] different [redacted] products in a randomised four period study. The packaging was controlled using two members of personnel, one performing the task and one checking. Reconciliation of product and labels was performed appropriately and the randomisation of each arm was reviewed. Line clearance was performed appropriately. Each trial subject has an allocated barcode number which is correlated with each pack using the [redacted]

C10 Quality Control

No QC testing is undertaken at the site.

C11 Contract manufacture and Analysis

Testing of starting materials is contracted out to [redacted] and detailed in an appropriate technical agreement. Environmental monitoring of the pharmacy assemble area is contracted out to [redacted]

C12 Complaints and Product Recall

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

C13 Self Inspection

A system audit of the pharmacy was planned for [redacted] and completed in Aug 2012. Two pharmacy system audits were planned in [redacted]. The [redacted] audit was completed in May [redacted] The scope of the system audits and details of any deficiencies identified were not reviewed during this inspection.

C14 Distribution and shipment

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

C15 Questions raised by the Assessors in relation to the assessment of a marketing authorisation

Not applicable.

C16 Annexes attached

Annex 1 site risk rating

SECTION D LIST OF DEFICIENCIES

D1 Critical

None

D2 Major

2.1 Change Control

The arrangements for prospective evaluation of change prior to implementation and the qualification of equipment was deficient in that:

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- The change control procedure [redacted] did not have sufficient control points to ensure any change was implemented safely e.g. there was one approval required at the start of the process and no subsequent approvals, for instance identification of prerequisites and approval of the completed change.
- There is no procedure to review or assess the introduction of new products to ensure that they do not present an unacceptable risk to the existing facility or trials.
- The Qualification of software and hardware procedure [redacted] was computer centric and did not me the requirements of EU GMP Annex 15 e.g. did not mention the requirements for User Requirement Specification, Design Qualification or Operational Qualification.
- The change control for the installation of a new safety cabinet and containment suite was deficient in that:
  - The change control was not raised until the 19th July 2012 despite quotes for the project being prior to this date
  - The project did not meet the requirements of EU GMP, for example there was no Design Qualification or User Requirement Specification
  - As there was no clear design specification it was not clear what the objective of the facility was or how this objective would be confirmed as met
  - The stated design of the facility was to have a higher pressure ante room to contain any contamination in the clean room, however the report from the contractors, [redacted], indicated that the air flowed out of the facility rather than being contained
  - The inlet HEPAs had not been integrity tested
  - The [redacted] protocol had not been preapproved to include predefined acceptance criteria
  - The Biological safety cabinet report did not include [redacted] tests so it was not clear how the cabinet had been qualified to achieve containment
  - The report for the safety cabinet had not been signed by a representative of Celerion
  - The change control indicated that the change had been implemented on 25th September 2012, however there were a number of outstanding items and no clear way to ensure completion of these items prior to using the facility

Reference: EU GMP Chapter 1, 1.4 (Xiii), 1.8 (ii) Annex 15, Principles, 2, 5, 6, 8, 9, 10, 43, 44

D3 Others

3.1 Deviation reporting

The control of deviation reporting was deficient in terms of the timeliness of reporting, close-out of investigations, and a lack of detail documented in the investigation report. For example:

- Deviation reports [redacted] contained insufficient detail of the investigation and actions taken to support the impact assessment and decision that no follow-up action was required. It was not evident how the non-conformity had been assessed as 'not high risk to

business' and therefore on what basis the decision not to escalate to a quality issue had been made

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- The system used to track the status of deviation reports was not robust as the electronic deviation reports indicated that Deviations [redacted] were not finalised. In addition, Deviation [redacted] appeared to be a duplicate report of Deviation [redacted]
- Deviation [redacted] identified a failure to calibrate and maintain the safety cabinet and isolator in a timely manner. This investigation was raised approximately 3 weeks after the event (event 6th March 2013 incident raised 26th March 2013). The investigation did not include a root cause investigation and did not therefore include and Corrective or preventative actions (CAPA).

Reference: EU GMP Chapter 1, 1.4 (ix), (xv), 1.8 (vii)

3.2 Training

Training was weak in that:

- The new pharmacy technician started working for the company 20th June 2012 but did not receive any formal GMP training until 13th September 2012.
- There was no robust system for ensuring employees do not perform tasks for which they have not received appropriate training.
- One of the QPs had no authorised Job description for the QP role.

Reference: EU GMP Chapter 2, 2.8 and 2.9

3.3 Personnel

The was a lack of evidence of QC and EU GMP experience documented in the CV, job description and associated training records to support naming [redacted] as Quality Controller on MIA(IMP) licence 15059.

Reference: EU GMP Chapter 2, 2.3, 2.6, 2.7 and Chapter 6, 6.1 and 6.2

3.4 Vendor Management

The control of vendors was deficient in that:

- There was no technical agreement in place with [redacted] for calibration of isolators, to outline the GMP related requirements and standards of work expected
- The installation and validation of the new biologicals containment suite was completed by [redacted] who are not listed as an approved pharmacy vendor.

Reference: EU GMP Chapter 1, 1.4 (vi), (vii) and Chapter 7 7.1, 7.4, 7.5, 7.14 and 7.15

D4 Comments

- It was agreed with the company that the variation to approve adding biologicals to MIA(IMP) 15059 would be put on hold until such time when the company are able to provide a revised validation package for a desktop review by the Inspectors. It is expected that the revised package will be submitted within 3 months and meet the requirements of EU GMP Annex 15 as referenced in deficiency 2.1 above.
- It was agreed with the company that the variation to name a new Quality Controller on MIA(IMP) 15059 will be reconsider in light of the deficiency referenced in 3.3 above. It is expected that the company will submit an amended proposal in response to the inspection deficiency.
- It is noted that the MIA(IMP) and the GMP certificate for the site authorise the aseptic processing of large volume, small volume and semisolid sterile products. The current facilities are only used for reconstitution and dilution of products in closed systems and

would not be acceptable for any more complex aseptic processing. It was agreed with the company that the aseptic process authorisation would have detailed restrictions applied to the certificate and the MIA. It is expected that the company will submit proposed wording for the restriction for review by the Inspectors.

SECTION E SUMMARY AND EVALUATION

E1 Closing Meeting

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

E2 Assessment of response(s) to inspection report

An initial response dated 11th July 2013 was received, which accepted the findings and proposed a revised validation package by 30th September 2013. A further status update dated 27th September 2013 was provided, which reported that the validation package would be delayed until October 2013. The information eventually supplied failed to answer all of the outstanding questions and concerns relating to the validation of the new biological containment suite.

The site were informed that the validation package did not comply with Annex 15 of the EU GMP guide and further clarification of MHRA's expectation for the validation package was provided by the Inspector on 12th December 2013. A further revised and updated validation package was submitted on 30th January 2014 and was assessed as satisfactory. The performance qualification (PQ) is on-going and it is expected that the PQ documentation will be regularly updated. The results obtained and any associated non-compliance and corrective actions will be reviewed during the next routine site inspection.

E3 Documents or Samples taken

None

E4 Comments and Evaluation of Compliance with GMP

The unit is broadly compliant with EU GMP.

SECTION F FINAL RECOMMENDATIONS/CONCLUSION

(refer to Annex 1 where applicable).

F1 Recommendations

Support the current licence, approve the variation and re-inspect at a 24 month frequency based on the specific risks identified in Appendix 1

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F2 Conclusion

The site is generally compliant with EU GMP. The current licence can continue to be supported. Variation MIA(IMP)15059-M-0019 to name [redacted] as Person Responsible for QC and to add biological manufacture can be supported.

SECTION G INSPECTORS' NAMES, SIGNATURES AND DATE

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Signed: [redacted] Dated: 18th February 2014

Lead Inspector:

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:	4	Last Inspection:	2

(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.		

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(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
	Other discriminatory factor (record details and justify below)

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(d). Inspectors Comments Related to Discriminatory Factors

[redacted]

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

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

(f). Conclusions

[redacted]

(g). Expert/ Operations Manager Comments (Risk rating level 0, I, II):

[redacted]

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

Rating:	Next Inspection due by:
[redacted]	