INSPECTION REPORT

Novartis Pharmaceuticals UK Limited
200 Frimley Business Park
GB- Frimley/Camberley, Surrey GU16 7SR
UNITED KINGDOM

Head Office:
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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MS 101 version 12, MIA (IMP) version 15, MIA 101 version 44, WDA (H) 101 version 3.

Licence Holder/Applicant: Novartis Pharmaceuticals UK Limited

Details of Product(s)/ Clinical trials/Studies:

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	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	N
Packaging - Secondary	N
Importing	Y
Laboratory Testing	N
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Other: *Import and Batch Certification of IMPs*	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 17/09/2015 to 18/09/2015 (1 day)

Lead Inspector: [redacted]

Accompanying Inspector(s): N/A

Case Folder References: Insp GMP/GDP/IMP 101/1135-0013.

Note to file: The Novartis Pharmaceuticals UK Limited site in Frimley held four authorisations. The site number on MS, MIA and WDA (H) was 1135. The site number on the MIA(IMP) was updated from 1803065 to 1135 on 09 November 2015, to be in line with the other authorisations on site. No other changes were made to the MIA(IMP); this change was for administration purposes only. The site number of Novartis Pharmaceuticals UK Limited in Frimley is 1135 and the company number is 101. Previous inspection history for MIA(IMP) was recorded in Insp GMP/GDP/IMP 101/1803065-0003, the MHRA casefolders have been linked.

Section B General Introduction

B1 Background information

Novartis Pharmaceuticals UK Limited is a subsidiary of Novartis Pharma AG., with headquarters in Basal, Switzerland. Novartis UK CPO (United Kingdom Country Pharma Operation) headquarters were located on site at Frimley. They site was responsible for sales, marketing and distribution of the all licensed UK product range, maintenance of product and site licenses and also provision of Medical Information services. At the time of the inspection, the site held four authorisations WDA(H), MS, MIA and MIA(IMP). Departments for Commercial Supply Chain activities, Drug Regulatory Affairs, Quality Assurance and Medical Information were located in Frimley. Production, warehouse and QC activities are subcontracted.

Following closure of Novartis Horsham in Q4 2013, QA responsibility transferred from Horsham to Frimley including batch release, artwork approval, QA complaints oversight, deviation approval, PQR review, change control, QA vendor oversight.

CPO UK was the EU batch release hub. At the time of the inspection, there were 171 MAH Novartis products marketed, 33% were National marketing authorisations held by Novartis Pharmaceuticals UK limited and CPO UK Frimley was the release site. Centrally authorised products (37% of MAH Novartis) were held by Novartis EuroPharm Limited and Novartis Nuremberg and CPO UK Frimley were the authorised release sites.

Novartis acquired GSK oncology portfolio in 2015, the GSK Oncology business franchise was integrated into Novartis Oncology franchise on 2 March 2015 (8 brands, 25 SKUs)

Previous Inspection Date(s): 23/10/2012 and 24/10/2012

Previous Inspectors: [redacted]

B2 Inspected Areas

Review of licences,
Review of completion of responses from last inspection

Quality Systems
Change control
Incidents/Deviations
Customer complaints
CAPA
Change Control
OOS
Risk Management procedure
PQRs

Product Recalls
Reject batches

Artwork Management

Documentation/Release procedure – QP Release & IMP QP Release
Technical agreements
Wholesale dealing/ GDP aspects

Bone fide checks of suppliers/customers Delivery arrangements Counterfeit awareness Computer system / inventory management Returns Importation Notifications to the MHRA

Limitations / exclusions to inspected areas

Particular Patient supply activity on site was limited and therefore not reviewed in detail. Training Self inspection

B3 Key Personnel met/contacted during the inspection

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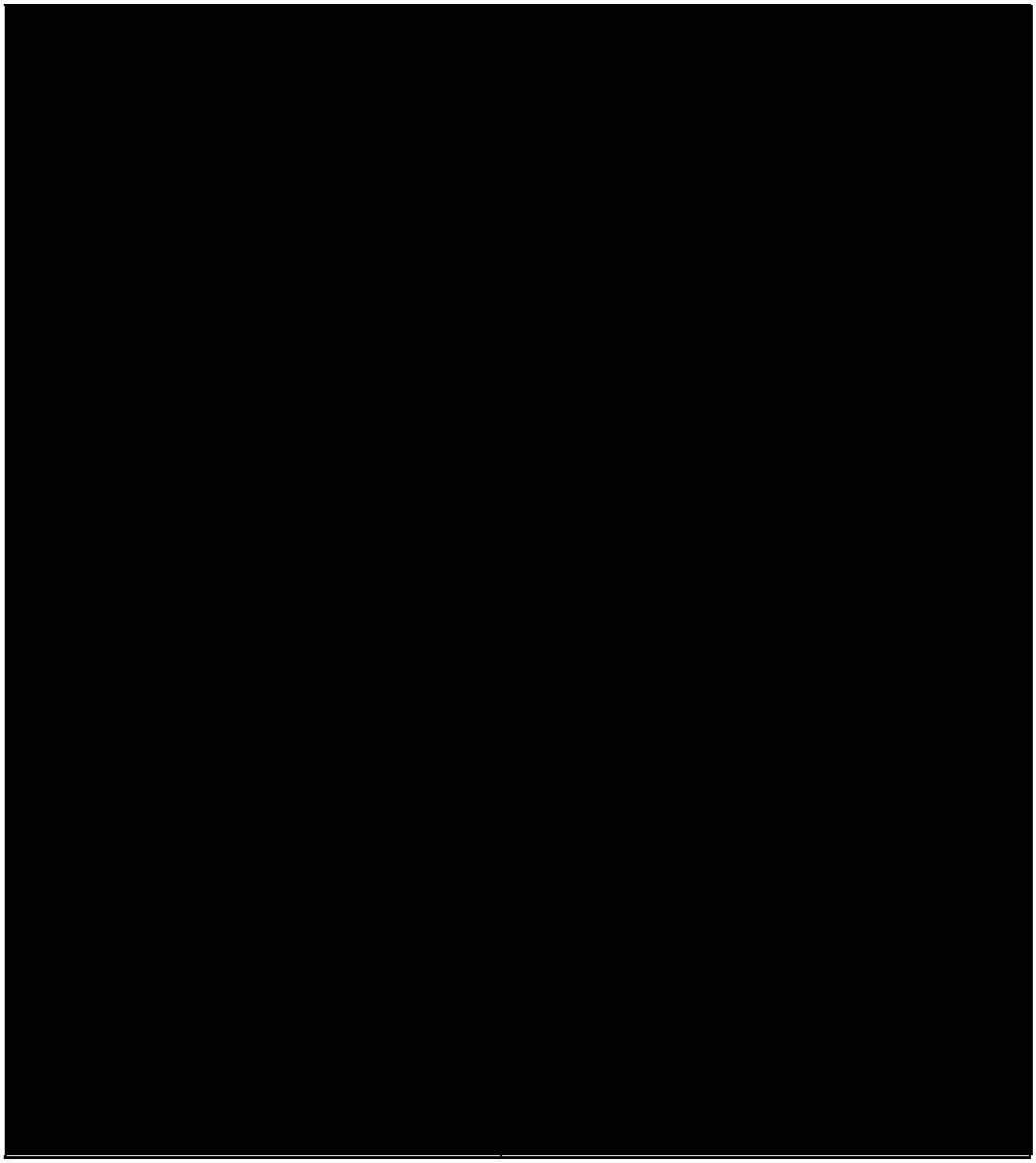

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[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	Version 3. Dated: 05.08.2015	Y/N
Compliance Report	Dated: 10.08.2015	Y/N
Comments: N/A		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes were recorded in the compliance reports held in the case folder.

Changes since Previous Inspection

- Following closure of Novartis Horsham in Q4 2013, QA responsibility transferred from Horsham to Frimley including batch release, artwork approval, QA complaints oversight, deviation approval, PQR review, change control, QA vendor oversight. CPO UK Frimley was the EU batch release hub.
- Novartis Pharmaceuticals UK had acquired GSK oncology products. The GSK Oncology business franchise was integrated into Novartis Oncology franchise on 2 March 2015 (8 brands, 25 SKUs)
- Senior Personnel changes including the CPO leadership team, as detailed in the compliance report and opening presentation.
- A new change control system on Agile and a new artwork control system on Artbase had been implemented.
- Authorisations had been updated to remove Horsham site and reflect personnel changes.

Changes were detailed in the compliance report, filed in the casefolder.

Future Planned Changes

No significant planned changes, reference compliance report.

C2 Action taken since the last inspection

The deficiencies raised at the previous inspection have been satisfactorily addressed.

C3 Starting Materials

General

Assurance of starting material was reviewed as part of the PQR process. Management of the process for the assurance of the starting materials was the responsibilities of the manufacturers Drug Supplier Management Group [DSM] located in Basel and East Hanover

Compliance with TSE Guidelines

The TSE process was reviewed and appeared to be satisfactory.

API Compliance

The DSM was responsible for API compliance.

C4 Pharmaceutical Quality System

Annual product Quality reviews were prepared by the manufacturing and packaging sites. UK CPO UK carried out formal reviews of the annual Product Quality Reviews (PQRs) for each product where they were the registered site of batch release. The ESO reviewed third party contract manufacturers PQRs and provided an executive summary to the CPO UK. There was a procedure [redacted] effective 21/12/3012 and form template [redacted] to detail the review and approval of the PQRs. The schedule for PQRs was tracked. The PQR for [redacted] was reviewed. The review period was [redacted] The manufacturing and packaging site was Novartis, Kurtkov. There was also a second packaging site in LEK Solvenia. A deficiency was raised as it was not clear if the releasing QP had full oversight and assessment of the remedial actions recommended in the PQR review which may impact ongoing batch release decisions, for example update to supplier technical agreements and an open global stability assessment.

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Deviations, change controls and complaints were managed electronically on AWQA system. Deviation Handling (AWQA System) [redacted], issued 04 January 2015 and associated system was reviewed. The SOP was unclear as to the definition of a reoccurring deviation. The root cause of deviations was not formally trended therefore it was not clear how it was determined that effective CAPA had been implemented.

A number of deviation records were reviewed including [redacted] and transport deviations [redacted] Transport deviations from [redacted] were tracked; they were raised as a QIR and recorded on the third party deviation report. A transport temperature deviation for dual product [redacted] was reviewed, a deficiency was raised as the CAPAs, risk assessment and handling of internal complaint [redacted] associated with this deviation were lacking. The internal complaint had been cancelled; there was evidence of a lack of control of the right to cancel a record in AQWA. Reference section D for details. .

Third party logistic sites [redacted]) were responsible for receipt, booking in, retention and storage of products received for Novartis. On arrival of the shipment, the third party logistic sites removed the relevant samples and performed the duty of care checks and sent the relevant paper work to QA at UK CPO for review. The Duty of Care and Regulatory Compliance checks completed in the UK CPO were detailed in [redacted] issued 17-Sep-2013. This information was part of the routine review as part of the EU batch release and certification as per [redacted]

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issued 09 September 2015. All IMPs were imported from [redacted] services. IMP QP release was particularly reviewed. There was no requirement in technical agreement with [redacted] services. Or in the batch release SOP to inform the IMP QP of all deviations before release of product. A deficiency was raised.

Novartis Pharmaceuticals UK Limited was the MAH for some [redacted] own label products. [redacted] was co-located on site in Frimley. QPs from Novartis Pharmaceuticals UK Limited certified some product (8 to 10) for [redacted] The technical agreement in place between the two companies was reviewed.

The change control process and examples of records including [redacted] was reviewed and deemed satisfactory.

The process for PSF and CTA management was briefly reviewed, no issued were raised.

Particular Patient Supply UK CPO [redacted] effective 19 August 2012 described how Novartis supplied investigational medicinal products currently unlicensed in the UK to individual patients with an unmet medical need. This process was briefly reviewed and no issued were raised. TSE certification process and checks on right to receive were reviewed and satisfactory. UK commercial Particular Patient supply [redacted] effective 07 February 2014 was also reviewed.

The notification system to inform the MHRA of the import of unlicensed products was reviewed and was satisfactory.

The process for Supplier and Customer Bona fide Checks was reviewed, the process was as per [redacted] A deficiency was raised as the SOP to requalify customers did not describe the type and frequency of checks to be made to confirm the validity and ongoing compliance with GDP of wholesalers' dealers. Reference section D.

AwOps Artwork Creation and Approval. [redacted] effective 11 August 2014 was reviewed. The process for generation and approval of artwork approval was sufficient.

C5 Personnel

There were 925 colleagues at the UK CPO. Personnel met during the inspection were knowledgeable and were able to explain all relevant key aspects of their roles.

C6 Premises and Equipment

Not applicable.

C7 Documentation

A global solution for archive of electronic batch documentation from the [redacted] had been implemented. A number of procedures had been updated following change in responsibilities in Frimley. There was a global requirement to review SOPs every three years.

C8 Production

No manufacturing on site. Products are manufactured by Novartis sites or third party manufacturers overseen by the External Supply organisation (ESO)

C9 Quality Control

There was no QC testing on site, three contract laboratories were in use at the time of the inspection.

C10 Outsourced Activities

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All vendors are included in a GMP vendor list managed by UK CPO QA unit. Contract manufacturers are managed globally by ESO (External supply Organisation) except [redacted] a secondary packaging site, which is managed locally. The Technical agreement (TA) with [redacted] dated March 2014 was reviewed, no issued were raised.

The supply chain group has a local SOP governing the management of GDP supplier/vendors. Local technical agreements are in place as required.

[redacted] was the primary third party logistics site. [redacted] was managed locally; oversight included weekly meeting and monthly KPIs. The TA was reviewed.

Fisher scientific was the third party logistics site for IMPs. [redacted] also offered manufacturing, and packaging, storage, distribution, and labelling services related to the clinical supply chain. The TA with [redacted] dated May 2014 was reviewed and was satisfactory.

C11 Complaints and Product Recall

UK CPO Management of Product Quality complaints, [redacted] issued 18 December 2014 was reviewed. This procedure described the process used to manage IMP and commercial product complaints. The UK CPO was also responsible for any complaints relating to Horsham manufactured or packaged stock. All product quality complaints were recorded and reviewed by Medical Information Services team on MI Quest and then the complaint was send to QA and logged in AQWA. The transfer system was audited to ensure no information was lost between the systems, this audit was documented but near misses were not tracked for training purposes. The Complaint was investigated locally and then escalated to manufacturing or packaging site for further investigation. If three or more complaints were received for the same batch the QP was informed via AWQA. Complaints were closed by the QP. Complaints were classified as Critical, Major and Minor. Complaint samples were verified by [redacted] device using Prove system where possible. The system was capable of confirming if the packaging was from a genuine Novartis product. Complaint trending was completed as a 12 month rolling trend. Trending for 2014 was reviewed, 219 complaints were raised in 2014, 13 were classified as justified. As of February 2015, 270 complaints had been raised in the previous 12 months. 18 were classified as justified. The trend reports for complaints were high level and it was not possible to fully determine if there was a batch level trend from the data recorded in the reports. In 2014, there was an increase in complaints for [redacted]. There was a spike of complaints received for [redacted] relating to product reconstitution and blocked needles following a formulation change to the diluent. A number of complaint records were reviewed including [redacted]

An internal complaint was defined within the global procedure as a complaint received from a Novartis manufacturing or non-manufacturing site before the product was brought to market or used in clinical schedule. A number of internal complaints were reviewed [redacted] and [redacted] A deficiency was raised due to failing in handling of complaint [redacted]

The returns process was reviewed and it was in-line with MHRA guidelines.

C12 Self Inspection

Not reviewed at this inspection.

C13 Distribution and shipment

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Third party logistic sites [redacted]) were responsible for receipt, booking in, retention and storage of products received for Novartis. The third party logistic sites removed the relevant samples and performed the duty of care checks on behalf of UK CPO.

[redacted] Procedure and requirement for the definition and maintenance of transport conditions for API and Drug Product was reviewed. Each product was risk assessed and assigned to a temperature classification based on stability data, specific transport controls were assigned to each transport classification. There was evidence the risk assessments were not being regularly reviewed to consider new information for example deviations, updated stability trend data. The [redacted] risk assessment was completed in 2005 and there was no evidence of a more recent review in line with QRM principles. A deficiency was raised.

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

2 MAJOR

2.1 Appropriate corrective actions and/or preventative actions (CAPAs) were not identified and taken to ensure the transport temperature conditions defined for dual product [redacted] were suitable.

2.1.1 [redacted] was subject to temperature excursion of below zero degrees [redacted] during transport. The batch [redacted] was rejected due to the potential impact on the integrity of the accompanying WFI ampoule. It was identified at the time that the company did not have appropriate stability data to support the assigned temperature transport condition of [redacted]" i.e. 2 to 8°C for this dual product. It was also identified that this temperature excursion was within the defined tolerance range as per [redacted]" labelled products and therefore as per procedure would not require investigation if it reoccurred.

The company failed to implement appropriate preventative actions to ensure further temperature excursions would be appropriately assessed for impact.

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2.1.2 An internal complaint raised on the temperature excursion of [redacted] was cancelled without documented justification. An Event raised on the issue was also closed without appropriate investigation with a view to taking an appropriate preventive action.

2.1.3 The risk assessment to define the temperature transport condition for dual product [redacted]t was not robust and did not fully consider the stability of the dual product including the WFI ampoule.

2.1.4 The risk assessments for temperature transport storage conditions was not kept up to day or regularly reviewed in line with principles of quality risk management [redacted] risk assessment was completed in 2005; there was no evidence of periodic review of the assessment following more recent deviations.

* Suitability of the assigned temperature transport conditions for all dual products subject to release in Frimley are to be reviewed.

D3 Others

3 OTHERS

3.1 **The Quality management system was deficient in that**

3.1.1 The trending of complaints was high level, the root cause of complaints was not reviewed in all cases when a trend was identified and therefore it was not possible to determine if appropriate measures had been taken in respect of defective products to prevent reoccurrence.

3.1.2 The Deviation [redacted] was unclear as to the definition of a reoccurring deviation. There was no formal process to trend the root cause of deviations, to assess for reoccurrence and therefore ensure that effective CAPAs had been implemented.

3.1.3 The review of [redacted] was deficiency in that;

3.1.4 There was no evidence Part A of [redacted] review for 2014 was a controlled document, it did not contain a reference to [redacted]

3.1.5 Part B, the QP review of [redacted] 2014 APR stated no future actions were required. There was a lack of evidence of QP assessment/review of the recommended actions in the APR, for example remediation actions related to supplier technical agreements or an open global stability assessment.

Reference: EU GMP Chapter 1 (1.8 (xi), 1.11), Chapter 4 (Principle, 4.1),

3.2 Assess control in AQWA computerised systems was deficient in that

3.2.1 There was evidence of a lack of control of the right to cancel a record in AQWA. There was no documented assessment of what level of access/permission was required to cancel a deviation, change control, CAPA or complaint in the electronic system.

Reference: EU GMP Chapter 4 (Principle, 4.1), Annex 11 (2)

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3.3 There was no requirement for deviations to be notified to IMP QP as part of batch release, e.g. there no procedural requirement for QP to review deviations in the IMP release SOP or there no requirement in the technical agreement with [redacted] to inform the IMP QP of deviations.

Reference: EU GMP Annex 13 (40,41)

3.4 The SOP to requalify customers did not describe the type and frequency of checks to be made to confirm the validity and ongoing compliance with GDP of wholesalers dealers, for example it did not include a review of a copy of customer's authorisations, detail of checks to be made on the Eudra database http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do or a review of the list of suspended and revoked licences for manufacturers and wholesalers of medicine.

Reference: GDP Guidelines 5.3.

D4 Comments

4 COMMENTS

4.1 Novartis Pharmaceuticals UK Limited casefolder to be updated to name [redacted] as site contact. Inspector to complete.

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]	
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The list of deficiencies was presented and accepted.

F2 Assessment of response(s) to inspection report

A satisfactorily response to resolve the issues identified during the inspection was received.

F3 Documents or Samples taken

Reference casefolder for details.

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

Within the scope of the inspection, Novartis Pharmaceuticals UK Limited operated in general compliance with the requirements of Directive(s) 2003/94/EC and in accordance with The Medicines For Human Use (Clinical Trials) Regulations 2004, The guidelines of 5 November 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01) and The Human Medicines Regulations 2012; thereby the GMP and GDP certificates will be issued.

Name and Dated Signature of Inspector (s):

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Signed: [redacted]

Name: [redacted]

Dated: 10 November 2015

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:	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.		

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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)

(d). Inspectors Comments Related to Discriminatory Factors

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

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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 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)

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[redacted]

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

Rating:	Next Inspection due by:
[redacted]	