DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	March 6-10, 13, 14, 2023
	FEI NUMBER 3011684330

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Daniel Van Plew, Executive Vice President and General Manager, IOPS

FIRM NAME	STREET ADDRESS
Regeneron Ireland Designated Activity Company	Raheen Business Park
CITY, STATE AND ZIP CODE Limerick, Ireland	TYPE OF ESTABLISHMENT INSPECTED Bulk Drug Substance Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1
The quality unit did not ensure issuance of documents is controlled and original records are maintained.

1. Original GMP forms are not retained. The routine practice across the site is to discard original GMP forms if there are mistakes or changes required after receiving feedback. The data from the discarded GMP forms is rewritten onto a new GMP form. This routine practice is not consistent with procedure SOP-GE1008 "Recording Data" which in section 8.1.7 prohibits destruction of original GMP forms.

Employees can print forms used for GMP recording from the Doc Compliance system. Although this software maintains an audit trail of what GMP forms are printed, the audit trail is not reviewed and the GMP forms are not reconciled to ensure printed forms are retained.

On March 7, 2023, there were (18) shredders available throughout the facility and accessible to employees. A shredder in a general office area was observed to contain unidentified shredded documents. Additionally, there were (48) confidential bins throughout the facility where employees can discard documents. There was no quality oversight to ensure that original GMP documents were not discarded in these bins. Review of (4) selected bins on March 7, 2023, identified the presence of discarded, original GMP forms. For example,

a. A partially completed template associated with AQ-PTCL-039822 (b) (4) Determination of Osmolarity by Freezing Point Osmometer Assay Qualification" for osmolarity testing data. Procedure GE-1022 requires templates used to record data in QC laboratory notebooks must be pasted into the notebook before any data is recorded. A second version of this form had been pasted into the notebook and used for reporting.

b. Partially completed Form QA2529 "Raw Material Release Checklist" for lot (b) (4) of (b) (4) Sterile Bag. A second version of this form was used for reporting.

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c. Two different partially completed versions of Transfer Deviation Form VA-6419 associated with a method transfer for (b) (4) (1.0). A third version was used for reporting.

d. QC Administrative Task Request Form IS-2348 for (b) (4) that requested addition of the (b) (4) to LIMS. A second version was used for reporting

e. Forms that had been initiated with a signature and date, but not completed including, but not limited to: Form QC-1553 "QC Chemistry/Biology Request Form", Form GE-2928 "(b) (4) Run Sheet", Form GE-5053 (b) (4) Scan Review Form", and Form MH-3 "Request for Shipment".

f. The presence of numerous blank documents that had been printed from the Doc Control system including, but not limited to: Form QA2529 "Raw Material Checklist", Form QA7 "Regeneron General Training Documentation Form", Form V11798 "QC Virology Sample Transmittal and Test Analysis Request Form", Form GE2396 "Request for Video in Support of GMP Activities", and Form GE-4586 "Active CAPA Revision Request".

2. Procedure SOP GE-1008 "Recording Data" permits original GMP forms to be discarded after they have been scanned, with only the scanned version being maintained. Scanning is done by the person that generated the form and there is no quality oversight to ensure what is scanned is complete and accurate. Review of scanned forms including QC Administrative Task Request Form IS-2348 for (b) (4) showed scanning was not always legible and review of Microbiological Environmental Analysis Form MI-1457 from May 21, 2021, showed recorded dates had been cutoff in the scan.

3. The procedure SOP GE-1008 "Recording Data" permits an individual to print scanned GMP forms and apply a wet signature. The individual will then rescan the document and discard the document with the original signature. There is no process to authenticate that all signatures are original and accurate.

4. Employees use uncontrolled "templates" during GMP activities. These templates are maintained on shared computer drives and discarded after use. The quality unit is not fully aware of what templates are being used throughout the facility. For example,

a. A template used to document QC data review. The template includes checklists and comments to identify what

corrections are required to the QC data or suggested manual integration parameters.

b. A template used to notify quality of a Notification of Event (NOE) was being used by production personnel. These templates are filled out by production personnel when they believe a NOE is required to be opened in the quality system. Quality personnel do not maintain these notifications or provide any documentation of their decision making process if they determine not to open an NOE within the quality system.

c. A template to document required corrections during logbook review.

5. Numerous notes made on equipment status tags were found in the discard bins. Included in these were notes that pointed out discrepancies in logbooks. These discrepancies were not corrected or captured as an NOE. The logbooks had already been signed as reviewed. For example:

a. Log 08315, (b) (4) Logbook". The note states page 4 verified box not N/A'd, but no boxes are missing the N/A and there is no documentation that a late entry had been made. The note also states page 5 (b) (4) initial and date is missing on cross out. This was still missing, even though the logbook had been reviewed on September 14, 2022.

b. Log 11141 V1.0 (b) (4) UV-Visible Spectrophotomer Logbook". The note stated on page 36 the description of task was missing. It was still missing, even though the logbook had been reviewed on March 30, 2022.

OBSERVATION 2
Scientifically sound test procedures are not established and followed.

Manual integration is routinely used for chromatography and capillary electrophoresis methods. Procedures are not followed to ensure documentation for the justification for using manual integration or to ensure adequate review.

1. Procedure SOP-QC3071 requires the analyst to attempt to optimize the automatic integration parameters before applying manual integration, but review of the electronic files showed no documented results demonstrating

attempts to optimize the integration parameters during the analysis. For example, sample (b) (4) (lot (b) (4) and sample (b) (4) (lot (b) (4) associated with CE-SDS testing of (b) (4) (b) (4)

If there are attempts to optimize automatic integration parameters or manual integration, no records are kept. Only the original system integrated result and the final result with manual integration changes are being saved and reviewed.

2. Within the Empower software used to process chromatography and capillary electrophoresis data, the analysts and reviewers have been given permission to see the peak area counts in the review window. This allows them to change integration while seeing how it affects the area counts, without requiring them to save the changes to the integration.

3. Procedure SOP-QC3071 requires a comment to adequately explain the reason for manual integration be put in the audit trail. Review of project folders showed general comments that could not justify the need for manual integration were being entered. For example,

a. Manual integration was used on the main peak of sample (b) (4) without justification for its need, as well as other peaks. The sample is associated with lot (b) (4) for (b) (4) during CE-SDS testing.

b. Manual integration was used on the (b) (4) peak of (b) (4) without justification for its need, as well as other peaks. The sample is associated with lot (b) (4) for (b) (4) during CE-SDS testing.

c. The project folders for (b) (4) CESDS_2022Q3a associated with CE-SDS testing of (b) (4) (b) (4) (1185 instances of manually integrated results), (b) (4) CESDS_2023Q1A associated with CE-SDS testing of (b) (4) (87 instances of manually integrated results), and (b) (4) iCIEF_2023Q1A associated with iCIEF testing of (b) (4) (82 instances of manually integrated results) applied the general comment of "Manually adjusted baseline to integrate peaks appropriately" to each result.

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4. There is no QA review to ensure consistent and accurate application of the procedures for manual integration.

OBSERVATION 3
Control records do not contain complete data derived from all tests.

The source electronic data, including audit trails, logs, or alarms has not been reviewed for production area manufacturing equipment or in-process testing equipment used during manufacturing of batches of US market product.

Review of electronic data from in-process testing equipment identified the following:

1. Review of the Solo VPE software for performing in-process (b) (4) readings in (b) (4) identified production employees were not reporting all test results into the batch record.

a. There are two test results in the electronic data for (b) (4) at the (b) (4) stage for batch (b) (4) of (b) (4) Only the second is recorded in the batch record, with no explanation for the first analysis.

b. There are two test results in the electronic data for (b) (4) on the Solo VPE in the (b) (4) area for batch (b) (4) of (b) (4) Only the second is recorded in the batch record, with no explanation for the first analysis.

There are a total of (b) (4) Solo VPE instruments in the production areas that have not required review of the electronic source data.

2. Review of the Nova (b) (4) electronic data in (b) (4) found the presence of batch testing that was not recorded in the associated logbook, including (b) (4) lots (b) (4) and (b) (4) There were QC check failures that were not recorded in the associated logbook and any corrective actions taken following the QC check failures were not recorded in the associated logbook. For example, on October 24, 2022; November 9, 2022; and November 23, 2022. Additionally, the logbook was not documented sequentially, but had reviewed and found to be acceptable on January 4, 2023.

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There are a total of (b) (4) Nova instruments in the production areas that have not required verification of electronic source data.

3. Review of the electronic data files for the filter integrity tester in (b) (4) found the presence of an aborted test associated with batch (b) (4) The aborted result was not included with the batch record as required by procedure SOP-MA733 "Operation and Maintenance of the Sartocheck Filter Integrity Testers".

There are a total of (b) (4) filter integrity testing instruments in the production areas that have not required verification of electronic source data.

OBSERVATION 4
Deviations from established procedures are not thoroughly investigated.

1. Investigation EOE22-0089 was opened after it was confirmed a QC employee had backdated multiple Form-QC2836 (b) (4) LIMS Continuity Chain of Custody Form" forms and signed with someone else's initials. The investigation was expanded to other laboratory logbooks and records to determine if there were similar events. However, this review only included review of the records, without using any techniques to cross reference entries that could detect backdating, such as verifying against electronic data, badge access records, or CCTV footage. There was no comparison of employee signatures in the reviewed records to the signature logs to authenticate the signatures.

During the EOE22-0089 investigation, review of LOG-09459 (b) (4) QC Stability Controlled Temperature Unit (CTU) Recording Logbook" identified numerous missing entries and GDP errors in logbooks that had already been reviewed and archived. These were documented in NOE22-04701. No investigation was initiated to evaluate why these discrepancies were missed during the original review or whether other records were not adequately reviewed.

2. Procedures to recognize trends in the quality system do not ensure trends are recognized in a timely manner. For example, when trending invalid QC results in LTIFs, trending only considers if the same analyst is involved (b) (4) times during the review period, without considering whether the same issue is being observed across multiple

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analysts or the number of times that analyst is performing the test during the review period. If there are similar occurrences captured in LTIFs and GLIFs, these are not captured in the trending review.

For example, there have been 808 LTIFs opened to invalidate testing during endotoxin analysis since March of 2021, of which 708 were attributed to "man", and an additional 40 GLIFs, of which 15 were attributed to "man". Repeated investigations identifying similar causes of "man" are closed without initiating timely actions.

OBSERVATION 5

Air handling systems are not appropriately monitored and appropriate action is not taken when limits are exceeded.

1. Areas of the (b) (4) Lab and Formulated Drug Substance Dispensing areas classified ISO 5 do not have non-viable particle data during dynamic operations to demonstrate that they can meet ISO 5 during operation.

2. Failures of HEPA filters are handled as Notice of Event (NOE), which doesn't require investigation of root causes. Since May 2021, there have been 9 HEPA filter failures in classified production areas. These HEPA filter failures have identified filter damage, but were not further investigated to determine what could have caused the damage and whether it could reoccur or impact other HEPA filters.

OBSERVATION 6

Data is not thoroughly reviewed by the quality unit.

1. Procedures for reviewing laboratory electronic data do not include sufficient detail and documentation to ensure all electronic records are reviewed or document what was covered during the review.

2 (b) (4) review of unlocked Empower project folders was not occurring for all unlocked project folders since January of 2022.

3. Procedures requiring periodic review of security and administrative settings are not specific to what needs to be checked for each software. For example, Empower, Solo VPE, or Nova (b) (4) testing equipment.

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4. QA reviews do not routinely include evaluation of source data in review of production or QC data.

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