

| <b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b><br><b>FOOD AND DRUG ADMINISTRATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                  |                                          |
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| <small>DISTRICT ADDRESS AND PHONE NUMBER</small><br>12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857<br>CDER-OC-OMQ-International483Response@fda.hhs.gov                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <small>DATE(S) OF INSPECTION</small><br>02/10/2025-02/20/2025*<br><hr/> <small>FEI NUMBER</small><br>3003600340                  |                                          |
| <small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small><br>Mr. Himanshu Saxena, Head – Biologics Manufacturing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |                                          |
| <small>FIRM NAME</small><br>Syngene International Ltd.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <small>STREET ADDRESS</small><br>Biocon Sez, Biocon Park, Plot No. 2, 3, 4 & 5,<br>Bommasandra Industrial Park, Jigani Link Road |                                          |
| <small>CITY, STATE, ZIP CODE, COUNTRY</small><br>Bengaluru, Karnataka, 560099, India                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <small>TYPE ESTABLISHMENT INSPECTED</small><br>API, Drug Substance, and Finished Drug Product<br>Manufacturer                    |                                          |
| <p>This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.</p>                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                  |                                          |
| <b>DURING AN INSPECTION OF YOUR FIRM WE OBSERVED<sup>1</sup></b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                  |                                          |
| <b>OBSERVATION 1</b><br>Reliability of components that could potentially impact products manufactured, are not established, or verified periodically, as part of the vendor qualification process.<br><br>Specifically,<br><br>Your firm does not perform verification of the data present on the certificate of analysis of critical consumables (bioburden, endotoxins, sterility, etc.). SOP-GMP-QAL-006, , “Vendor Qualification Procedure for Commercial Supply in (b)(4)”, version 8, effective: 3 Feb 2025, step 7.1.2.1.3, defines critical consumables as “Consumables which will have direct contact with (b)(4) Drug Substance (DS) or Drug Product (DP) and may directly affect the SISPQ (Safety, Identity, Strength, Purity, and Quality of the Product)”. Critical consumables are accepted for use in (b)(4) upon document review of the Certificate of Analysis.                                                                                       |                                                                                                                                  |                                          |
| <b>OBSERVATION 2</b><br>Lack of an adequate environmental monitoring program.<br><br>Specifically, <div style="margin-left: 20px;">             A. Area qualifications and classifications do not place an emphasis on data generated in dynamic conditions. Your firm’s represented area classifications, detailed in “Area Classification and Pressure Zoning – (b)(4) Version 004, approved Oct 24, 2024, are based on data measured in static conditions or “at-rest” and not in periods of activity or in “dynamic” conditions. The in-operation classifications of production areas in (b)(4) are not equivalent to the classification in static conditions, specifically, area Environmental Monitoring data routinely establishes the respective areas as lower classification level in dynamic conditions, than they are qualified, at-rest. (b)(4) Formulated Drug Substance and (b)(4) Formulated Drug Substance are manufactured in (b)(4)           </div> |                                                                                                                                  |                                          |
| <b>SEE REVERSE OF THIS PAGE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Marcellinus D Dordunoo, Investigator<br>                                                                                         | <small>DATE ISSUED</small><br>02/20/2025 |
| <small>FORM FDA 483 (09/08)</small>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                  |                                          |



| <b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b><br><b>FOOD AND DRUG ADMINISTRATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |                                                                                                                                  |  |
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| <small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small><br>Mr. Himanshu Saxena, Head – Biologics Manufacturing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |                                                                                                                                  |  |
| <small>FIRM NAME</small><br>Syngene International Ltd.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  | <small>STREET ADDRESS</small><br>Biocon Sez, Biocon Park, Plot No. 2, 3, 4 & 5,<br>Bommasandra Industrial Park, Jigani Link Road |  |
| <small>CITY, STATE, ZIP CODE, COUNTRY</small><br>Bengaluru, Karnataka, 560099, India                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | <small>TYPE ESTABLISHMENT INSPECTED</small><br>API, Drug Substance, and Finished Drug Product<br>Manufacturer                    |  |
| <p>B. Dynamic monitoring of classified areas in (b)(4) (b)(4) and support areas (b)(4) is not performed during all production operations. For example, viable monitoring via active air sampling is currently only performed at rest, prior to operations.</p> <p>C. Your firm's current personnel monitoring practices are deficient. Microbiology and In-Process Quality Assurance personnel do not perform any personnel monitoring in classified areas, during support of production operations. For example, during production of (b)(4) (b)(4) Formulated Drug Substance, Batch No. (b)(4), on Jan 19, 20225, only one production operator has documented personnel monitoring, despite both QC Microbiologist and IPQA personnel being present in the classified areas during set-up, EM, and postproduction operations. However, according to SOP-GMP-QCM-0027, Section 7.4, Environmental Monitoring (EM), Microbiologists along with IPQA personnel, perform the transport of EM materials ((b)(4) plates) to the (b)(4) areas. No routine personnel monitoring data is available to assess the (b)(4) behaviors and practices of QC Microbiologists and IPQA personnel in classified production areas.</p>                                                                                                                                                                                                                                                                                                                                                                                                            |  |                                                                                                                                  |  |
| <p><b>OBSERVATION 3</b><br/>           Failure to adequately investigate any nonconformances.</p> <p>Specifically,</p> <p>While reviewing Environmental Monitoring (EM) records for the (b)(4) production of (b)(4) (b)(4), BMR-GMP (b)(4) OPS-830002590-0002, (b)(4) (b)(4), Batch No. (b)(4) I observed a missing entry for passive air monitoring, an apparent EM excursion in the (b)(4) area, and missing personnel monitoring data. However, I noted that when the firm's personnel enter multiple rooms, they document the time of each relative sampling. For this event, the Microbiologist and IPQA, documented entry in (b)(4) and sampling times of "1326/1327" and "1320/1322" respectively. The firm's OOS investigation concluded that both the Microbiologist and IPQA, entered the (b)(4) (b)(4), did not perform (b)(4) as no actions were performed in (b)(4) then performed (b)(4) upon exiting the (b)(4) area, and mistakenly documented the (b)(4) of the (b)(4) monitoring section of the record. I expressed concern that the firm ignored the documented evidence, and generated an alternative root cause, that although possible, is contrary to the documented entries made by the personnel themselves, at the time. Additionally, the firm was unable to explain how (b)(4) that should be labeled with the collection time, person from who they were taken, and the grade of the area, could be mixed up. No pictures of the incubated plates with labels were included in the investigation. According to your Microbiology personnel, these plates were disposed of, as OOS had occurred.</p> |  |                                                                                                                                  |  |
| <b>SEE REVERSE OF THIS PAGE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | Marcellinus D Dordunoo, Investigator<br>                                                                                         |  |
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| <small>FORM FDA 483 (09/08)</small>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |                                                                                                                                  |  |
| <small>PREVIOUS EDITION OBSOLETE</small> <b>INSPECTIONAL OBSERVATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |                                                                                                                                  |  |
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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                             |                                                                             |
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| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED<br>Mr. Himanshu Saxena, Head – Biologics Manufacturing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                             |                                                                             |
| FIRM NAME<br>Syngene International Ltd.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | STREET ADDRESS<br>Biocon Sez, Biocon Park, Plot No. 2, 3, 4 & 5,<br>Bommasandra Industrial Park, Jigani Link Road           |                                                                             |
| CITY, STATE, ZIP CODE, COUNTRY<br>Bengaluru, Karnataka, 560099, India                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | TYPE ESTABLISHMENT INSPECTED<br>API, Drug Substance, and Finished Drug Product<br>Manufacturer                              |                                                                             |
| <p><b>OBSERVATION 4</b></p> <p>Controlled Documents are not secure and properly managed to prevent unauthorized changes or access.</p> <p>Specifically,</p> <p>While reviewing Environmental Monitoring (EM) records for the (b)(4) production of (b)(4) (b)(4) BMR-GMP (b)(4) OPS-830002590-0002, (b)(4) (b)(4) Batch No. (b)(4) -I observed a missing entry for passive air monitoring, an apparent EM excursion in the (b)(4) area, and missing personnel monitoring data, I asked the firm's management team to explain the noted deficiencies. Your firm's QC Microbiology personnel later provided additional EM records. However, upon review the documents provided were the same document filed in the production batch record, but contained additional information, not present on the version that had been signed and dated reviewed by QA and QCM (dated: 18 Nov 2020). The version filed in the batch record and provided to investigators with the hardcopy batch record, contained no notations regarding the numerous entry errors, and single deviation related to the excursion and missing personnel monitoring data. However, contained handwritten headers, identifying them as attachments to the batch record, dated: 09 Dec 2020. The firm was unable to explain how a reviewed document in possession of the quality unit, could contain entries, not present on the hard copy filed with the batch record documentation, also not present at the time of review. The information added were employee ID numbers. Evidence of executed, and reviewed batch record documentation that can/have been accessed and modified without detection by the control systems the firm currently has in place, subverting quality system controls, are counter to the expectation that records are contemporaneous and accurate.</p> <p><b>OBSERVATION 5</b></p> <p>Classified areas are deficient in that ceilings are not smooth and/or hard surfaces that are easily cleanable.</p> <p>Specifically,</p> <p>Classified areas in the (b)(4) manufacturing suite, located on the (b)(4) floor of the (b)(4) Production block, are equipped with (b)(4) HEPA filters (b)(4) into (b)(4) panels. However, this mounting position exposes the (b)(4) material of the (b)(4) to the (b)(4) environment, production areas used in the manufacture of (b)(4) Formulated Drug Substance and (b)(4) Formulated Drug Substance. The (b)(4) exposed (b)(4) provides a difficult to clean, harboring</p> |                                                                                                                             |                                                                             |
| SEE REVERSE<br>OF THIS PAGE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Marcellinus D Dordunoo, Investigator<br> | DATE ISSUED<br>02/20/2025                                                   |
| FORM FDA 483 (09/08)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATION                                                                          | Page 3 of 5                                                                 |

| <b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b><br><b>FOOD AND DRUG ADMINISTRATION</b>                                                                                                              |                                                                                                                                  |
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| location for contaminants and microorganisms to harbor. The (b)(4) manufacturing suite also house (b)(4)<br>(b)(4)                                                                                 |                                                                                                                                  |
| <sup>1</sup> Observations 1, 2, 3 and 5 are specific to manufacture of Formulated Drug Substance: (b)(4)<br>(b)(4) and (b)(4)<br>(b)(4)                                                            |                                                                                                                                  |
| <b>*DATES OF INSPECTION</b><br>02/10/2025 (Mon), 02/11/2025 (Tue), 02/12/2025 (Wed), 02/13/2025 (Thu), 02/14/2025 (Fri), 02/17/2025 (Mon),<br>02/18/2025 (Tue), 02/19/2025 (Wed), 02/20/2025 (Thu) |                                                                                                                                  |
| <b>SEE REVERSE<br/>OF THIS PAGE</b>                                                                                                                                                                | Marcellinus D Dordunoo, Investigator<br>      |
| <small>DATE ISSUED</small><br>02/20/2025                                                                                                                                                           |                                                                                                                                  |

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."