DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

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.

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

OBSERVATION 1

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing. Specifically,

A) Review of source data for samples analyzed as part of Biosimilarity Studies (b) (4) and (b) (4) Reference Standard Qualification, generated in KC4 plate-reader software, identified inconsistencies in the recorded dates of actual plate readings with the dates of creation and last modification of their electronic data files. Specifically, inconsistencies were observed between 1) plate read date recorded and file created date, 2) file created date and file last modified date, and/or 3) file last modified date preceding file created date. However, audit trail functions fail to capture any changes made to each KC4 file or to the data within each KC4 file.

B) A total of (b) (4) individual bioassay plates analyzed 25JUL, 30JUL, 01AUG, and 06AUG2014 on plate-reader RD/AN-05-135 with KC4 software, using (b) (4) Lot (b) (4) as a reference standard ((b) (4) % RP, or (b) (4) IU/mL per COA), were used to qualify (b) (4) Reference Standard Batch (b) (4) against (b) (4) medicinal product batches.

The issuance and maintenance of equipment/instrument logbooks at that time of Biosimilarity Studies (b) (4) and (b) (4) Reference Standard Qualification of Batch (b) (4) was described by Rev. 04 of SOP SP-QA-050 (eff. 30SEP2013). Section 6.6 specifically required that logbook entries include associated batch numbers while Section 6.10 specifically required information be entered concurrently and in chronological order. However, review of the instrument logbook for plate-reader RD/AN-05-135 identified numerous entries lacking batch numbers, non-sequential hand-written entries, and no # of samples/plates analyzed per entry.

C) Biosimilarity Study (b) (4) was performed assuming (b) (4) % potency (label claims) of the (b) (4) Medicinal Product, EU (b) (4) Batch (b) (4) used as a reference standard. Each batch analysis performed to support Biosimilarity Study (b) (4) was performed by R&D without documentation of test execution on Data Recording Sheets and reference to the (b) (4) Batch (b) (4) was not handwritten onto the assay template/coversheets, dated 05DEC2011, by analyst (b) (6) until 19DEC2011. Details of the cell line, reagents, and the equipment and

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	10 May 2017	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017

instrumentation used, sample preparation activities, and system suitability was not documented for batches analyzed for Biosimilarity Study (b) (4)

OBSERVATION 2

Appropriate controls are not exercised over computers or related systems. There was a failure to maintain a backup file of data entered into the computer or related system.

Specifically,

A) Review of the audit trails of source data files for Biosimilarity Study (b) (4) dentified numerous sequential plate readings as follows:

• 071211,raw data.xpt

Plate (b) (4) read (b) (4) times from 23NOV-07DEC2011

Plate read times from 23NOV-07DEC2011

Plate read times from 25NOV-07DEC2011

• 081211,raw data.xpt

Plate (b) (4) read (b) (4) times from 25-08DEC2011

Plate read times on 08DEC2011

Plate read time on 08DEC2011

Management explained that the practice of opening existing data files, renaming the data files for new analyses, and running of sample plates resulted in the audit trails capturing multiple plate runs. Successive plate runs for data files 071211,raw data.xpt and 081211,raw data.xpt are traceable to the equipment usage logbook for Equipment ID RD/AN06-224 used according to date/time, however specific Batch #'s are not documented and the quantities of samples recorded do not reconcile. Since .xpt files consist of no batch identification until source data is transcribed into .xls templates and Softmax software, and test data from that period unrelated to biosimilarity studies, including .xls templates and PLA calculations were not retained, there are no means of verifying the identity of samples in the successive plates runs.

B) According to SOP SP-QC-231-02, chromatographic sequences are to be initially saved in C:\Chem32\... filepaths with transfer settings referencing the corresponding OpenLAB server remote data path per Section 6.2.26. After analyzing samples, data is to be loaded from the appropriate OpenLAB DataStore sequence container (SC.SSIZip folder). Upon integration, individual chromatograms are to be saved according to their

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: Jaspreet Singh, Vice President Quality	
FIRM NAME Intas Pharmaceuticals Ltd.	STREET ADDRESS Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	TYPE OF ESTABLISHMENT INSPECTED Biosimilar Sterile Drug Manufacturer

respective sequence of injections (e.g. C:\Chem32\[Instrument #]\DATA\data2016\[Product Code]0000001.D, -2.D, -3.D, etc.) per Section 6.2.40. The push of data files to the OpenLAB DataStore is not automated, and required only after saving of all chromatograms as per Section 6.2.42.

The ChemStation "Guide for Administrators" explains the system's Transfer Management Settings for "Manage queue on connect" and "Cleanup on Shutdown". It states that selection of the latter option "deletes all local data and sequence files that have been stored in the central repository. Methods and sequence templates remain on the local file system."

1) Numerous batch analysis and system check sequence files (.S format) identified in the current, active C:\Chem32\1\SEQUENCE\ and C:\CHEM32\2\SEQUENCE\ directories have no corresponding OpenLAB DataStore sequence container or individual .S files;

2) Individual file metadata for these sequences is inconsistent with that of .S files of the same names, identified in OpenLAB DataStore SC.SSIZip folders corresponding to the same dates of analysis.

C) Performance verifications of the current Chemstation/OpenLAB CDS software and OpenLAB DataStore server were documented by the Equipment Qualification Report "OpenLAB-OQ" on host IBM438 (rev. SW.01.84, eff. 25-26APR2014). Software qualification consisted of a "BIOOPENLAB" server connectivity test.

Automatic Data Transfer Settings are required to be selected in order for the "OQAdmin" user to run the server connectivity test. The "ChemStation: Settings" instruction specifically state to "Take a screenshot of the current configuration and restore it after the qualification is finished." As these settings are configured as a Data Store pre-requisite prior to qualification activities, no screenshots of the settings prior to or after the server connectivity test were recorded.

Management stated that the selection of all Automatic Data Transfer Settings is fixed by IT administrators, under the operating system "Admin" and "Administration" users, prior to approval of the system for QC laboratory use.

Modifications to ChemStation administrative settings, specifically Automatic Data Transfer Settings, are not captured in ChemStation or OpenLAB system logs. The operating system's application log does not capture changes made within ChemStation Administration Tools module. And the operating system & security logs are not queriable for "Admin" or "Administrator" actions or logins.

Review of the current settings of the ChemStation Administration Tools module for Workstation 438 identified 2 of the 4 radio buttons for Automatic Data Transfer Settings unselected. Namely, the automatic transfers of source data files to the OpenLAB DataStore upon 1) data modification and 2) import after reprocessing were not enabled for Workstation 438.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	DSC 10MAY2017 RP	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

D) Chemstation/ChemStore software was used to perform all HPLC analysis thru implementation of Change Control 50455, initiated 20JUN2014. Change Control 50455 consisted of revision of each applicable standard test procedure to include the 14JUL2014 revisions of TP-QC-324 (rev. 03) for reverse phase-HPLC, TP-QC-325 (rev. 03) for size exclusion-HPLC, and TP-QC-326 (rev. 03) for (b) (4) -HPLC of (b) (4) drug substance, drug product, and stability testing. Impurity testing performed prior to JUL2014 lacks system/project/ sequence/injection audit trails, established user control groupings & assignments, defined user control group privileges, and system & security configurations to ensure the integrity of chromatographic data generated and processed using Chemstation/ChemStore.

E) Upon request, data generated JAN-JUN2014 on workstation IBPL/QC/D165 (identified in a decommissioned IT equipment storage room), which serviced HPLCs QC-06-121/HPLC-04 and QC-06-122/HPLC-05 using legacy Chemstation/ChemStore software, was restored from backup.
Review of the directories and data files from the JAN-JUN2014 restore from workstation IBPL/QC/D165 identified series of "Single Runs", each named "SNAPSHOT.D", which appeared to correspond chronologically with the last sequences run during each month. Management explained that historically "snapshots" were taken of injections during test sequences for the purposes of integrating sample data (b) (4) (i.e. (b) (4) a test sequence). According to Quality Control management, this off-line processing of curve data (b) (4) was performed to evaluate if the run was performing as expected.
Acquisition of the June 2014 snapshot data file for HPLC-04 (C:\Chem32\2\DATA\IBPL-QC-D165\IBPLHPLC\1 \DATA2014\JUNE14\SNAPSHOT.D) is documented at (b) (4) hrs. on 26JUN2014. Reconciliation of this time point identified its occurrence between completion of the single "System Check" injection of sequence SCJU1426 (SCP12000001.D) at 16:35:00hrs. and the initiation of test sequence QC140626 (P12SEC0000001.D) at (b) (4) hrs., yet there is no injection data file corresponding to the snapshot taken at (b) (4) hrs.

F) On April 26, 2017, we discovered a loose spreadsheet and email attachment dated June 20, 2015 located in the IT Store Room that stated: "As per our yesterday's discussion please create a back-up for the HPLC data for the following mentioned HPLC details. Please create a back-up according to new data path and for HPLC-23 data is most priority the computer ID for HPLC-23 was IBM 233. Once you found please copy all the data in the computer ID IBM172 D:\ drive." At the bottom of the spreadsheet, the document further states for computer IBM 233: "No data found once data found please copy data in computer ID IBM172 D:/ drive (most priority)". The

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	DSE 10MAY2017	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017

system was noted as "dumped" on December 15, 2014 in the HPLC 23 equipment logbook. During this inspection, all of the electronic data generated on the instrument prior to the dump was missing without any associated quality incident report filed for this missing electronic data. The logbook for this instrument shows that it was used for testing in process samples, peptide mapping, stress and oxidation testing for samples and (b) (4) (b) (4) chromatography analysis for (b) (4) (b) (4) mg/ml), (b) (4) ((b) (4) mg/ml), (b) (4) Drug Substance (b) (4) mg/ml), and (b) (4) (b) (4) .

OBSERVATION 3
The control records are deficient in that they are not an accurate reproduction of the appropriate control record that is checked for accuracy, dated and signed.
Specifically,
Section 6.2 of SP-QC-051-06, "Management of Data Recording Sheet" (eff. 15FEB2014), requires general DRSs to be generated by QA with a stamp identifying the original issuance. Each issuance is to be documented on a Form F/SP-QA-040.2 for respective analysis. For in process, batch release, and stability studies, DRSs are to be printed from SAP against the specific inspection lot per BPP/QM/014. BPP/QM/014 provides specific instructions on the business process used to issue DRSs from the firm's SAP system; it does not provide further instruction on the control of documents after printing.

A) The issuance of each DRS on Forms F/SP-QA-040.2-06 note only the number of copies required (total # of pages not documented). Forms F/SP-QA-040.2-06 are loose-leafed, unbound sheets and there is no sequential log of the issuance of documents used to record original test data used in Biosimilarity Studies (b) (4)

B) DRSs for bioassay of Batches (b) (4) were generated by QA Executive "VS" and stamped "ISSUED" with a date of 28OCT2013. Unused rows for additional entries (3 total) were not striked through at the time of form completion and remained available for additional entries as of 27APR2017.

C) Documentation for Batch (b) (4) was recorded in the DRS issued for U.S. (b) (4) Batch (b) (4) The DRS for U.S. (b) (4) Batch (b) (4) was generated by QA Executive "VS" and stamped "ISSUED" with a date of 28OCT2013. The Form F/SP-QA-040.2-06 for U.S. (b) (4) Batch (b) (4) references an unsigned/

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	TYPE OF ESTABLISHMENT INSPECTED Biosimilar Sterile Drug Manufacturer

unannotated .xls printout identifying the DRS issue requests for several analyses of several batches to include U.S. (b) (4) Batch (b) (4)

- Although analysis of both batches is documented on the same DRS, there is no reference to the inclusion of Batch (b) (4) on the Form F/SP-QA-040.2-06 for the DRS of U.S. (b) (4) Batch (b) (4)
- Although analysis of both batches is documented on the same DRS, there is no reference to the inclusion of CA (b) (4) Batch (b) (4) on the Form F/SP-QA-040.2-06 for the DRS of Batch (b) (4)
- Although analysis of both batches is documented on the same DRS, there is no reference to the inclusion of US (b) (4) Batch (b) (4) on the Form F/SP-QA-040.2-06 for the DRS of Batch (b) (4)

D) DRSs printed directly from SAP are copy-controlled by the # of pages identified in the footer of the original print and the inclusion of a block letter, grayscale "ORIGINAL" watermark. Management explained that the block letter, grayscale watermark appears darker in black & white photocopies than in original prints. Review of various DRSs throughout the inspection, both of documents in use and photocopied upon request to be provided as exhibits, identified negligible if any readily identifiable difference in the watermarks between original prints and photocopies.

E) QC/CAPA/113 was initiated 10JUN2016 to capture Quality Improvement Plan (QIP) references to QC lab operations. QIP line items 156 and 178 specifically describe 1) the restriction of photocopy functions and 2) the locking of network connection boxes in various QC functional areas, specifically the QC Biochemical Section and QC Analytical/HPLC Lab, performed by IT personnel on 19NOV2016. This included the disabling of photocopy and scan functions of the Kyocera Ecosys FS-6525MFP multi-function printer located in the firm's Sample Management room. Challenging of the current copy & scan settings confirmed these IT restrictions. However,

- Attempts to scan on the FS-6525MFP noted that scanned files are assigned a default prefix: "doc";
- The FS-6525MFP's "Scan to" directory identified 3 personal folder paths, with Login User Name "administrator" and a 10-digit hidden password pre-filled for each, along with a single e-mail address pre-programmed;
- Review of the FS-6525MFP's "Send Job Log" (consisting of scanned files to be sent to various network folder destinations/e-mail addresses) identified 4 pages of files (consisting of 4 entries each), dated 26-28JUL2016, named in the format of "doc" followed by a 6-digit job ID, the 8-digit date (YYYYMMDD format), and the 6-digit time (HH:MM:SS format);

For example, the final 28JUL2016 entry of the Send Job Log consisted of filename "doc164386 20160728

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	10 MAY 2017	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

105332" scanned to one of the pre-programmed personal folders.
• Further review of the FS-6525MFP "System Menu/Counter***Counter – Scanned Pages" identified 34,782 pages scanned for "Copy" and 15,705 pages scanned for "Others" (50,587 pages total).

F) The firm's QC office, which is adjacent to and also utilized by the firm's Quality Head, consists of a second Kyocera multi-function printer, Kyocera Ecosys M2035dn. Similarly, management stated that both copying and scanning functions are currently disabled. Challenging of the current copy & scan settings confirmed these IT restrictions. However,
• Review of the M2035dn's "Send Job Log" identified scanned files through (b) (4) hrs. on 27APR2017 (filename "doc047910 20170427 (b) (4) 11");
• Further review of the M2035dn's "System Menu/Counter***Counter – Scanned Pages" identified 26,643 pages copied for print and 18,640 pages copied for scan.

OBSERVATION 4
Laboratory records do not include the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.
Specifically,
A) Review of source data for impurity testing (RP, SE, and (b) (4) methods) of 24M and 36M real-time stability samples of (b) (4) PPQ batches identified each data set being manually integrated. Steps for manual integration are described in each method's respective standard test procedure, and actual integration events applied are documented only in the processed revisions of data files. The review of analytical data generated for 24M and 36M stability timepoints of (b) (4) PPQ batches was described by SP-QC-082 (rev. 06, eff. 12JAN2015). Section 6.3.10 required that "Authorized-QC person/Section in charge shall check for correctness & completeness as well as calculations the respective DRS with all the raw data like chromatogram, calculation sheet…"
While requiring review of raw data for "correctness & completeness", it is silent on any specific requirement to review electronic source data or metadata. There is no documented review of the electronic source data for 24M and 36M RP-, SE-, and (b) (4) -HPLC impurity testing of (b) (4) PPQ batches, to include unprocessed data, the appropriate manual integration of each sample curve, or sequence/injection audit trails.

B) The current rev. 07 of SP-QC-082, eff. 01DEC2016, consists of the addition of Section 6.3.13 which requires

"Trained –QC person/Section in charge/Reviewer" to "review all electronic raw data as well as audit trail in the computer system by logging in the software along with printed raw data of respective DRS". However, secondary review of the manual integration applied to RP-, SE-, and (b) (4) -HPLC impurity sample curves is not documented.

C) The stability study (Report # ASSR-G503-QC-257-01) of (b) (4) drug product ((b) (4) mg/(b) (4) mL) under accelerated condition reports the total impurities by RP-HPLC analysis as (b) (4) %. The acceptance criterion for the total impurities analysis is (b) (4) %. Review of the electronic source data indicates that the chromatogram for this run sequence (G5030010-6MAT, injection date: 20-Mar-2016) was manually integrated. Section 6.3.13 of SP-QC-082-07 (effective date: 01-Dec-2016) states "Trained QC person/Section in charge/Reviewer…" to "…review an electronic raw data as well as audit trail in the computer system by logging in the software along with printed raw data of respective DRS". However there is no documentation of the secondary review of the electronic source data of the manual integration performed for this run sequence.

OBSERVATION 5

Written records of investigations into unexplained discrepancies do not always include the conclusions and follow-up and extension to other batches.

Specifically,

Incidents such as sequence interruptions or cancellations were not required to be documented until implementation of Rev. 00 of SOP SP-QC-273, "Procedure for Handling of Laboratory Incidents and Out of Specification (OOS) Results" (eff. 10OCT2016). Section 6.2 required the reporting and supervisory notification of obvious errors (b) (4) (b) (4) of analyses or incomplete testing/results with specific examples listed in Appendix B. Appendix B specifically identifies stopped or aborted sequences, system suitability failures, and instrument and/or software errors as examples of incidents. Section 6.15 of SP-QC-273-00 (Section 10.0 of the current SP-QC-273-01, eff. 26APR2017) explicitly requires analysts to obtain approval of the Head of QC prior to invalidating test data due to system suitability failures, aborted tests, suspended tests, etc.

A) Prior to the 10OCT2016 implementation of SP-QC-273-00 the firm's handling of OOS results was described by SP-QA-021 (rev. 08, eff. 19JAN2015). SOP SP-QA-021 consisted of no requirements for documentation of laboratory deviations or incidents which did not result in OOS results nor secondary approval of the invalidation of test data due to aborted, interrupted, or incomplete sequences. Management further stated that at that time no

other procedures documentation or secondary review & approval of such lab incidents or the invalidation of test data due to interrupted and/or aborted tests.

B) A post (b) (4) system suitability failure was observed for %RSD of 1 of (b) (4) reference standards (Reference Solution (b) (4) (b) (4) ng/mL) during SE-HPLC testing of (b) (4) Batch #'s (b) (4) (b) (4) for release. The QC Lab Supervisor's review of the SST failure and the QC Lab Manager's authorization for re-analysis was documented in Lab Incident Logbook SP-QC-273-00 on 04MAR2017. The DRS request for re-analysis was submitted 08MAR2017 and re-analysis was initiated on 10MAR2017, yet

- calculated totals of the original data set were not prepared until 10MAR2017;
- hard-copy prints of chromatograms and the compiled calculation sheet were not documented as checked by a second QC Lab Supervisor until 15MAR2017;
- there is no audit trail function or documented histories of initial and final, compiled revisions of .xls calculation sheets
- the sequence audit trail for the original data set identifies no secondary review of source, electronic data.

There is no documentation of QC lab management verifying the SST failure, either in printed, hard-copy or electronic form, prior to authorization of the re-analysis of (b) (4) Batch #'s (b) (4) (b) (4)

C) The written process was not defined for the handling of retesting for Out-of-Specification results generated prior to SOP SP-QC-273-01 entitled Procedure for Handling of Laboratory Incidents and Out of Specification (OOS) Results dated April 26, 2017.

For example, OOS 80115 that was closed on March 28, 2017 for (b) (4) Drug Substance (b) (4) explains that during data recording sheet (DRS) review, it was observed that estimated potency of Plate (b) (4) is (b) (4) % and is not complying with the specification (b) (4) %- (b) (4) %) of stated potency. However, the (b) (4) of all (b) (4) is within the specification. The assignable root cause for the OOS result was not determined but the hypothetical root cause was determined to be method variation that caused the OOS result. A reanalysis plan was proposed testing samples in (b) (4) using (b) (4) different analysts. The retest results were found within specification. The original OOS result was then invalidated and the final reported results from the acceptable retest were reported for the sample.

In addition, OOS 70085 that was closed on October 21, 2015 for raw material (b) (4) batch

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

(b) (4) explains that the growth promotion test for (b) (4) does not comply with the acceptance criteria mentioned in the specification and the result was observed at (b) (4) at (b) (4) with an acceptance criteria for optical density of more than (b) (4) at (b) (4). The OOS investigation did not determine an assignable root cause. The investigation further mentions that a retest is recommended because the same vendor lot number was received earlier dated May 22, 2015 that was complying with all of the specifications. The investigation also explains that further decision shall be taken based on the retest result. However, the retest plan was never defined and the remaining sample was then retested (b) (4) time. The retested sample had an acceptable result that was meeting specification. The original OOS result was then invalidated and the final reported result from (b) (4) sample retest was reported for the sample.

D) The re-investigation report for the deviation # 40186 (Attachment-21, dated 22-July-2015) includes an investigation of an additiona (b) (4) observed at the (b) (4) in the (b) (4) analysis at the (b) (4) (b) (4) stage of the batch (b) (4) The page-6 of this investigation report states, "Historical review of (b) (4) samples of batches (b) (4) to (b) (4) executed in year 2010 to 2011 was carried out. New peak was not observed in any of the samples analyzed by different analysts using TP-QC-006 except (b) (4) (b) (4) ", (b) (4) (b) (4) However review of the (b) (4) of the next batch (b) (4) shows a similar (b) (4) peak at the same (b) (4) and the above investigation was not extended to the batch (b) (4)

OBSERVATION 6

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically,

The most-recent air flow pattern test (smoke study) of the (b) (4) filling line's laminar air flow (LAF) unit, equipment ID FP12-0036, was performed 07JUL2015 by a vendor as documented in Report FP/AFV/07/15/001.

A) Video clips are captured, compiled, and edited to include subtitled descriptions of various scenes by the vendor under the direction of QA. Review of the compiled & edited filling LAF footage identified 8 different scenes, however original video files were not retained for verification of the original, unedited/cropped footage. The

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	DJR 10MAY2017 BP	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017

report result and conclusion identifies video compilation by a QA Sr. Executive, review by a QA Executive, and approval by a QA Manager. It is not specified whether review and approval of the smoke study is based on original or spliced, edited video footage.

B) The service vendor's SOP AVS/DOC/SOP/AFV/01, "STANDARD OPERATING PROCEDURE FOR AIR FLOW VISUALIZATION TEST", states the following: The test are performed till a proper airflow pattern is established as per the mutual agreement between the supplier and the buyer. In order to get the desired flow pattern, adjustments in velocities at the air supply and air exit are done till the acceptable flow pattern is established". The studies' edited video footage includes a scene of (b) (4) FP18-0036-MQ-01 reading a differential pressure between the LAF's (b) (4) and HEPA filter of (b) (4) nm of (b) (4)
Report FP/AFV/07/15/001 consists of no documentation of the air velocity/LAF damper settings at the time of the smoke study and edited video consists of no uninterrupted stream of footage showing that cross-filter differential pressure is maintained within normal operating limits at the time of demonstrating laminar air flow.

C) Report FP/AFV/07/15/001 consists of no documentation of the line speed used to simulate dynamic conditions during the demonstration of laminar air flow.

OBSERVATION 7
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.
Specifically,
A) Active viable air sampling is taken (b) (4) the aseptic (b) (4) finished product filling operations are performed in the aseptic manufacturing area. However, there is no active viable air sampling being performed when the actual aseptic filling operation is being performed in the aseptic area.

B) Environmental monitoring out-of-limit investigation EM-OOL-AC-MS-16-003 dated May 27, 2016 for a microbiological out-of-limit for the Grade A classified Media Room (LFH) Laminar Air Flow Hood was deficient. Regarding this, (b) (4) CFU (Staphylococcus arlettae) was found on a settle plate located in the Grade A classified Media Room (LFH) Laminar Air Flow Hood (BM16-0229) during the manufacture of (b) (4) batch (b) (4) (b) (4) However the investigation was deficient in that there was no product quality impact assessment made to

determine the impact of this microbiological out-of-limit on the product being manufactured at the time of this occurrence.

C) The microbial isolates trend analysis (b) (4) summary report for the period of (b) (4) dated January 19, 2017 states to perform a disinfectant study with the following four (4) in-house isolates: Staphylococcus epidermis, Kocuria variants, Bacillus cereus, and Ralstonia mannitolytica. However, Evaluation of Efficacy of Disinfectant Solution using in-house isolates study dated April 15, 2017 only tested Staphylococcus epidermis, Kocuria variants, Bacillus cereus, and substituted Sphingomonas Paucimobilis in lieu of testing Ralstonia mannitolytica without any written rationale for this decision to substitute the recommended isolate for testing. In addition, this Evaluation of Efficacy of Disinfectant Solution using in-house isolates study dated April 15, 2017 failed to perform a percent recovery of positive control during the execution of this study. Procedure entitled, "Evaluation of Efficacy of Disinfectant Solution dated January 18, 2017 states that (b) (4) % recovery of the in-house challenge microorganism positive control is required as a part of the acceptance criteria for performing the Evaluation of Efficacy of Disinfectant Solution. However, this positive control recovery study was not performed when executing this Efficacy of Disinfectant Solution study.

D) On April 27, 2017, we discovered that growth promotion testing (GPT) and release of microbiological plate media batches in the quality control testing laboratory was being performed in parallel and at the same time as environmental monitoring and use of these plates in the production area. The media plates were being used for environmental monitoring in the production area prior to the receipt of acceptable GPT results.

E) On May 4, 2017, during a walk-through of the quality control testing microbiology laboratory, we observed that the overhead HEPA filters used in the Grade B sterility testing room had an unknown (b) (4) discoloration. This room contained the laminar air flow hood unit that is used for finished drug product sterility testing.

F) On May 1, 2017, we discovered that the time and temperature during (b) (4) of media as well as the temperature of the media during media plate (b) (4) was not being recorded. SOP SP-QC-013-15 "Receipt, Preparation, Sterilization, Growth Promotion Incubation and Release of Micro Media" dated February 18, 2017 states that (b) (4) of media should occur at time (NMT (b) (4) and temperature (b) (4) °C) and media plate (b) (4) should occur at (b) (4) -(b) (4) °C. However, these temperatures and times were not being recorded. The (b) (4) media is used for the preparation of media used for bioburden testing and the media plates are used for various

microbiological tests at the facility.

G) Microbiological (b) (4) sampling procedure SP-QC-041-10 effective date January 25, 2017 states in section 6.3.2.1 to perform the (b) (4) method for (b) (4) using sterile (b) (4) (b) (4) as a diluent. However, the method suitability evaluation for this method performed under VP-QC-046-00 dated March 7, 2015 was performed using a different diluent (sterilized (b) (4)

OBSERVATION 8
Laboratory Controls do not include the establishment of scientifically sound and appropriate standards, sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity strength, quality and purity.
Specifically,
A) On April 27, 2017, during a walk-through of the quality control testing laboratory, we discovered that test procedure TP-QC-320-02 entitled "To lay down standard testing procedure (STP) for the determination of biological activity of (b) (4) by in-vitro bioassay" dated November 21, 2016 states in section 8.3 that both the Perkin Elmer Ensprire plate reader or the Biotek Gen 5 plate reader can be used for bioassay analysis. However, there was no equivalency study performed demonstrating that the results generated on these two (2) instruments are equivalent.

B) On April 26, 2017 during a walkthrough of the quality control testing laboratory, we observed that there was no printer attached for the microbalance QC06-109 that is used for pipette calibrations. In addition, this microbalance has the ability to be password protected to preclude changes to the settings within the instrument. However, this password protection option has not been enabled for this microbalance used in the quality control testing laboratory.

C) On April 27, 2017, during a walk-through of the quality control testing laboratory, we discovered that on April 24, 2017, there were six (6) bioassay samples ((b) (4) (b) (4) analyzed on the Biotek Gen 5 plate reader ID No RD/AN05-135. However, these samples were entered into the wrong logbook corresponding to the Perkin Elmer Ensprire plate reader serial number 2300 0992. There was no corresponding incident report for these samples entered into the wrong logbook.

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

OBSERVATION 9

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed. Specifically,

A) Failure to follow SOP-QA-040-09 entitled "Handling and Retention of Documents and Records" dated August 31, 2015. This procedure states that documents supporting the computer system validation should be retained in the Quality Assurance area. However, on April 26, 2017, we discovered Quality Assurance stamped forms with original handwritten data that was being retained in a stack of loose paper located in the IT Store room. These QA forms were for the Data Backup of Validated Computer System in GMP Area dated March 2016, April 2016, and May 2016.

B) Failure to follow SOP-QA-094-00 entitled "Status Labeling" dated November 21, 2016. This procedure states that the status of materials as well as equipment used at the facility should be labelled. On April 26, 2017, during a walk-through of the gas cylinder storage area, we observed a storage bank of (b) (4) gas cylinder bank that was unlabeled and received on the night of April 25, 2017 at the facility. These cylinders were not tested and released for use by the quality unit and were unlabeled with its identity and status. Furthermore, we also observed unlabeled nitrogen gas cylinders that were staged for use for quality control testing purposes. In addition, we also discovered an (b) (4) gas cylinder connection manifold that was still under installation and was not labelled with its designated non-operational status.

C) Failure to follow SOP SP-QC-101-06 entitled "Operation of Precision Balance, Analytical Balance and Microbalance" dated October 15, 2013. This procedure states in section 6.33 to 6.38 to calibrate the pipettes used at the facility using Picasso Software. However, this software was not available at the time of this inspection and was discontinued at the facility according to Change Control 51252 dated March 10, 2017. This procedure was never updated to reflect this change.

D) SOP SP-EN-010-04 entitled "Procedure for Breakdown Maintenance" dated February 10, 2017 does not require quality oversight or periodic review for equipment breakdown maintenance. Regarding this, Breakdown maintenance request forms (F/SP-EN-010.3-01) that are used to document equipment malfunctions in the production area are not reviewed by the Quality Unit. The user or operator of the broken equipment is instructed

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: Jaspreet Singh, Vice President Quality	
FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

on this form to determine the impact on GMP product and whether it is necessary to notify QA of equipment breakdowns.

OBSERVATION 10

Buildings used in the manufacture, processing, packing or holding of drug products are not free of infestation by birds.

Specifically,

On April 26, 2017, we observed numerous pigeons perching along the walls, dangling overhead wires and ceiling in the packaging material storage warehouse. This warehouse contained primary packing materials including (b) (4) that can be used to fill the (b) (4) drug product, secondary packing material including (b) (4) and (b) (4) used to store the final commercial drug product and (b) (4), consumable materials including (b) (4) tubing, filters used in the production area, (b) (4) (b) (4) bags and QC materials including empty petri plates and dishes as well as (b) (4) funnels. During the walk-through, we observed pigeon feces on the boxes containing the pre-sterilized empty petri plates and dishes.

OBSERVATION 11

Cell banks were not maintained under appropriate storage monitoring conditions designed to maintain viability and prevent contamination and records of the use of the vials from the cell banks and storage conditions were not maintained.

Specifically,

On May 2, 2017, during a walk-through of the bio-bulk manufacturing (BBM) area, we found that there was no continuous temperature monitoring being performed for the master and working cell bank storage (b) (4) temperature freezers RD/AN11-605 (Master Cell Bank (b) (4) °C Freezer) and BM-03-501 (Working Cell Bank (b) (4) °C Freezer). The temperatures are recorded (b) (4) for these freezers that store the master and working cell bank vials.

In addition, we also discovered that there was a discrepancy in the amount of working cell bank inventory for (b) (4) (b) (4) batch (b) (4). The maintenance and Issuance Record of Master Cell Bank/Working Cell Bank stated that there were (b) (4) vials in inventory inside (b) (4) temperature freezer BM-03-501. However, the physical inventory in this freezer showed that there were (b) (4) vials.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	DSR 5/02 10MAY2017	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Food & Drug Administration, CDER/Inspection Assessment Branch White Oak Building 51, Room 4235, 10903 New Hampshire Avenue Silver Spring, MD 20993, Attn: Mr. Concepcion (Coki) Cruz; Telephone 001-301-796-3254; FAX: 001-301-847-8738; E-MAIL: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 26, 2017-May 10, 2017
	FEI NUMBER 3007277149

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Jaspreet Singh, Vice President Quality

FIRM NAME	STREET ADDRESS
Intas Pharmaceuticals Ltd.	Plot No. 423/P/A, Sarkhej-Bavla Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Moraiya, Taluka Sanand, Ahmedabad, Gujarat 382 213 India	Biosimilar Sterile Drug Manufacturer

OBSERVATION 12

Procedures describing the calibration of instruments, apparatus, gauges and recording devices are not written or followed.

Specifically,

The scale that is used in the quality control raw material packaging laboratory to measure the length and width dimensions according to incoming product label specifications is not calibrated. In addition, a procedure has not been established for the calibration of this scale.

OBSERVATION 13

The quality control unit lacks responsibility to approve all procedures or specifications impacting the quality of drug products.

Specifically,

On April 26, 2017, during a walk-through of the (b) (4) generator plant equipment EN/07/0040 that is used in the (b) (4) system (b) (4) we discovered an (b) (4) measurement procedure that was prepared and reviewed by the engineering group and was not reviewed and approved by the quality unit. This test procedure was being used to periodically test the concentration of (b) (4) present in the (b) (4) system. In addition, the sample vial that is used for this (b) (4) test procedure was observed in an unclean status with remaining residual colorimetric sample left over from the previous (b) (4) test that was performed.

OBSERVATION 14

Employees are not given training in the particular operations they perform as part of their function.

Specifically,

There is no required training for outside contractors performing equipment maintenance and calibration activities inside the aseptic area. For example, on April 14, 2017, calibration of the mobile laminar air flow hood (b) (4) gauge was performed inside the aseptic area by an outside calibration company. However, the person performing the calibration activities within the aseptic area was only required to complete a health declaration form prior to escorted entry into the aseptic area.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	10 MAY 2017	Daniel J. Roberts, Investigator Patric C. Klotzbuecher, Investigator Bijoy Panicker, Investigator	05/10/2017