DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION
Food and Drug Administration-CDER/OC/DMPQ/ICT Attn: Alicia Mozzachio 10903 New Hampshire Avenue, Bldg 51, Room 4234 Silver Spring, MD 20993 Industry Information: www.fda.gov/oc/industry	alicia.mozzachio@fda.hhs.gov Phone: 001-301-796-3206 Fax: 001-301-847-8738	1/11/16 - 1/15/16
		FEI NUMBER 3002806754

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Claudio (NMI) Rebuzzini, President

FIRM NAME	STREET ADDRESS
Cosma SpA	Via Colleoni 15/17
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
24040 Ciserano, ITALY	API Manufacturer

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

Observation 1
Failure to maintain complete data derived from all testing and to ensure compliance with established specifications and standards pertaining to data retention and management. Specifically,

1. Data can be overwritten and/or deleted on 4 out of the (b) (4) HPLCs and 2 out of (b) (4) GCs used in the testing of APIs manufactured for the U.S. market. These systems do not have audit trails or password protection for individual operators.
2. Of the (b) (4) HPLCs, (b) (4) GC and (b) (4) FTIR computer systems with audit trails, there is no procedure describing the review of these audit trails and audit trails are not being assessed during the review of analytical data.
3. Data can be deleted off of the FTIR used in the testing of APIs. The data can be deleted off of the computer system's hard drive, outside of the system software and therefore not captured by the system's audit trail.

Observation 2
(b) (4) water used in the (b) (4) manufacturing steps of non-sterile APIs intended for use in further processing to produce a sterile drug product is not monitored and controlled for objectionable organisms. This material is accepted upon suppliers COA. Evidence that analyses was conducted on at least three batches before reducing in-house testing could not be provided. The reliability of the suppliers COA is not checked at regular intervals. This is a repeat observation from the 2013 FDA 483.

Observation 3
The specifications for the two non-sterile APIs (b) (4) USP) intended to be used in further processing to produce sterile drug product to not contain specifications for microbiological and endotoxin analysis.

Observation 4
Failure to maintain complete data derived from all testing and to ensure compliance with established API

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specifications and expectations pertaining to data retention. Specifically, your firm lacked sufficient information to evaluate the quality of your APIs due to the failure to maintain complete raw data from testing. Electronic records for chromatographic data are not available prior to 2011. This affects 23 of the 35 process validations still being referenced in support of (b) (4) DMFs.

Observation 5
Quality was not performing the following activities:

1. The GC system is not proven as suitable prior the running of residual solvents samples. System suitability is run after the samples are injected. This holds true for the residual solvents analysis for all API products for the U.S. market.
2. The HPLC system is not proven as suitable prior to the running of Enantiomeric Purity of (b) (4) API.
3. Cleaning logs for production equipment or for the sampling/dispensing room are not controlled, issued or tracked by Quality. Logbook pages can be copied from the procedures by production personnel as needed.
4. Electronic chromatograms are not reviewed during the release of analytical data. In addition, not all analytical data sheets used by QC analysts during the testing of APIs are documented as reviewed.

Observation 6
The following cleaning discrepancies were noted during the review of equipment used in the manufacturing of APIs:

1. (b) (4) spot checking is performed in support of cleaning validations. The spot checking of equipment used in the manufacture of non-sterile APIs intended to be further manufactured into sterile drug product do not address microbiological and endotoxin contamination. This is a repeat observation from the 2013 FDA inspection.
2. Production equipment was released for use prior to cleaning samples being analyzed. This was observed during the review of cleaning documentation for EV2 (b) (4) for lot (b) (4) dated 1/13/16. The (b) (4) was released based on a review of the cleaning batch record and visual inspection as the reviewer was unaware swab and rinse samples were taken and needed to be acceptable prior to the release of the equipment.
3. Operators do not document the amount of solvents or (b) (4) water used during the execution of cleaning records.
4. Justification that the length of the production campaign performed prior to cleaning did not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity

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profile could not be provided

5. The (b) (4) blow of water hoses to ensure the hoses are anhydrous prior to capping and storage is not document.
6. A log is not kept of the raw materials sampled and dispensed in the sampling/dispensing room and therefore it is unknown whether cleaning procedures are executed when needed. In addition, the cleaning procedure for the sampling/dispensing room does not specify what needs to be cleaned nor does it document what cleaning solutions where used.

Observation 7

During the review of stability monitoring of APIs the following discrepancies were noted:

1. Methods used during stability testing have not been proven to be stability indicating. The stress studies performed on methods used to analyze (b) (4) and do not support the conclusion that these methods can detect all of the impurities generated.
2. Microbial and endotoxin testing is not included in the stability studies performed for (b) (4) and (b) (4) These APIs are intended for further manufacturing into sterile finished drug products and are given a (b) (4) retest date.
3. During the review of the stability program it was noted packaging materials used to package stability samples and the number of stability samples packaged is not documented. There is not reconciliation of stability samples at the conclusion of the stability program.

Observation 8

The following discrepancies were noted during the microbial testing of the (b) (4) water used in the testing and cleaning of APIs manufactured for the U.S. market.

1. The total microbial count (TMC) microbial method has not been validated.
2. Growth promotion testing has not been performed on the media used during the execution of the TMC
3. There is no data to support that the current monitoring frequency of the microbiology incubator of (b) (4) (b) (4) will ensure that the samples remain within the established temperature ranges throughout the incubation process. The incubator is set at (b) (4) – (b) (4) °C and not 30 – 35°C as specified in USP.

Observation 9

The following discrepancies were noted during the review of production activities:

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1. Raw data is not retained during the weighing of the three individual tare weight used to obtain the average tare weight used during packaging. This was observed during the review of (b) (4) lot (b) (4) Although the average was recorded as (b) (4) the firm subtracted (b) (4) during the final packaging of the API.
2. Documentation is not performed contemporaneously during the execution of batch records. Production operators document time requirements to the nearest 5 minutes.

Observation 10

The following discrepancies were noted during the review of the maintenance and calibration program:

1. Schedules of maintenance and calibration are not managed through change control. The frequency of the maintenance and calibration of equipment is tracked using Database Maintenance software. Changes to this program are not tracked and can be performed by the Safety and Maintenance Manager.
2. Raw data is not retained during the execution of equipment calibrations. Raw data is destroyed after being entered into the Database Maintenance program.
3. The (b) (4) speed of the (b) (4) is deemed as critical during the production of (b) (4) however, the (b) (4) speeds are not routinely evaluated. (b) (4) 26 was used in the manufacture of (b) (4) on 9/28/15. Step (b) (4) specifies the (b) (4) speed needs to be set to maximum. The OQ of (b) (4) 26, performed in 4/2006 defines the maximum (b) (4) speed as ((b) (4) ± (b) (4)). The (b) (4) speed of (b) (4) is not part of the calibration program has not been evaluated since 2006.

Observation 11

Training files do not contain details to ensure personnel are trained on the particular operations performed. Specifically, finishing department operators were documented on being trained in the cleaning of equipment without detailing what equipment was covered. There are (b) (4) types of equipment in the finishing department. Documentation could not be provided that (b) (6) and (b) (6) were trained on the cleaning of EV2 (b) (4) even though they performed the cleaning of EV2 on 1/7/16. The version of the procedure being trained on is not documented and training is not provided to operators on revisions to master production batch records and master cleaning records.

Observation 12

Working copies of cleaning batch records are not exact copies of the master records. Specifically, the header

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templates used in the printing of master and working copies of cleaning batch records contain different information. The header template used in the working copies is not approved during the approval of the master cleaning record.

Observation 13
API product labels intended to be transferred outside the control of the manufacture's material management system do not contain the retest date or the name and address of the manufacturer.

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