GMP Drug Warning Letters Issued in Calendar Year 2015
Data Integrity Deficiencies
January, 2016

The tabulation on pages 4-54 include full text of data integrity deficiencies identified in FDA drug GMP warning letters issued in calendar year 2015. Links to the warning letter on the FDA website are included as well as information regarding imposition of import alerts posted on the FDA website. The nature of the products manufactured by the site, either API or dosage form, are also included along with date of publication of the warning letter, and the country in which the site(s) that are the subject of the warning letter are located. Specific text is highlighted in yellow, but this is not meant to be the entire text associated with the data integrity deficiencies. If forms 483 associated with the warning letter are available for purchase at the *FDAzilla store*, links are provided.

Of particular note:

- FDA issued 50 drug GMP warning letters in calendar year 2015. Twenty-seven (27), 54% of the total, were issued to compounding pharmacies, all located in the US. This continues FDA's extraordinary inspection and enforcement focus on this industry segment which began in 2014.
- A total of nineteen (19) drug GMP warning letters were issued regarding inspections outside the US; fifteen (15) of those included data integrity associated deficiencies. Thus, **79 % of warning letters issued regarding drug site(s) outside the US included data integrity associated deficiencies.**
- Three warning letters associated with data integrity reference inspections of multiple company sites.
- All of the drug manufacturing sites where data integrity deficiencies were identified are **located outside the US**, primarily in India which received 10 of the 15 (67%) warning letters. This is likely due to the increased focus on India and China as the primary suppliers of APIs and dosage forms sold in the US. Two of the fifteen (15) warning letters were issued regarding firms in the EU (the Czech Republic and Italy) two went to firms in China and one went to a firm in Thailand. The location of firms outside the US that received a warning letter that did NOT include data integrity deficiencies were issued to firms in Canada, New Zealand, Hong Kong and India.
- Of the fifteen firms that received warning letters associated with data integrity, five (5) manufacture drug product, seven (8) manufacture API and two (2) manufactures both API and drug product
- The **interval between inspection and warning letter issuance has generally increased significantly** as the year progressed. In at least several cases, FDA acknowledged that firms brought in third party firms as consultants to assist in remediation. It suggests that even with third party assistance, some of the firms were not making adequate progress.
- Virtually all deficiencies addressed herein focus on the laboratory instrument associated computers / software or failure to contemporaneously record data. The deficiency from the Sun Pharmaceuticals warning letter (deficiency

#6 in the warning letter) focuses on **manufacturing instrumentation associated software and computer systems**. While related deficiencies have occasionally been identified in past warning letters, the clarity of focus in this deficiency may represent an additional focus that inspectors will take in evaluation of manufacturing computer systems other than SAP. Watch for more of this in 2016 as FDA potentially expands their scope to include more manufacturing floor computer systems.

- Several of the warning letters with data integrity deficiencies were issued to sites that manufacture drug product and include deficiencies in aseptic processing. The **dual set of deficiencies in data integrity and aseptic processing seem to almost ensure a warning letter**. This is not a new trend for 2015 and was also found in previous years warning letters.
- Seven of the warning letter included **requirements that approached consent decree like requirements**. These requirements may be found in the listing of the specific deficiencies on pages 4-55 of this report. Companies involved include Micro Labs Limited, Apotex Research Private Limited, Hospira Spa, Yunnan Hande Bio-Tech Ltd, Sandoz Private Limited, Cadila Healthcare Limited, and Shejiang Hisun Pharmaceutical Co., Ltd.

Data Integrity Associated Warning Letters Issued in CY 2015:

Date of WL Issue	Company	Product Type	Date of Inspection(s)	Approximate Interval inspection to WL	Country
Jan. 9, 2015	Micro Labs Limited	Drug product	May 5-10 and May 12-13, 2014	8 months	India
Jan. 30, 2015	Apotex Research Private Limited	Drug product	June 23-July 1, 2014	7 months	India
Feb. 27, 2015	Novacyl Ltd	API	April 21-25, 2014	10 months	Thailand
Mar. 31, 2105	Hospira Spa	Drug product	May 5-9 and 12-13, 2014	10 months	Italy
Apr. 6, 2015	Yunnan Hande Bio-Tech Ltd	API	Apr. 14-17, 2014	12 months	China
May 27, 2015	VUAB Pharma a.s.	API	June 9-13, 2014	12 months	Czech Republic
July 13, 2015	Mahendra Chemicals	API	May 19-24, 2014	14 months	India
Aug. 16, 2015	Mylan Laboratories Limited (3 sites)	Drug product	Aug 1-8, 2014 Sept 23-Oct 3, 2014 Feb. 6-13, 2015	6-12 months	India

Sept. 2, 2015	Pan Drugs Ltd.	API	July 14-18, 2014	13 months	India
Sept. 28, 2015	Unimark Remedies Limited	API	Mar. 18-21, 2014	18 months	India
Oct. 22, 2015	Sandoz Private Limited (2 sites)	API	Aug 25-29, 2014 Aug 12-28, 2014	14 months	India
Nov. 5, 2015	Dr. Reddy's (3 sites)	API and drug product	Nov. 17-21, 2014 Jan. 26-31, 2015 Feb 26-Mar 6, 2015	8-12 months	India
Dec. 17, 2015	Sun Pharmaceuticals Industries Ltd.	Drug Product	Sept. 8-19, 2014	15 months	India
Dec 23, 2015	Cadila Healthcare Ltd. (2 sites)	API and Drug Product	Aug 28-Sept 5, 2014 Dec. 1-6, 2014	12-15 months	India
Dec. 31, 2015	Shejiang Hisun Pharmaceutical Co., Ltd.	API	March 2-7-2015	10 months	China

Similar analyses of data integrity associated warning letter deficiencies and form 483 observations have been prepared for the time periods of 2008 (with some earlier items) through 2014. Please contact Barbara at bwunger123@gmail.com for additional information**.**

Date	Company	Country	Text of Compliance	Import Alert
9-Jan-15	*Micro Labs Limited* (drug product)	India	**1.Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).** Our inspection identified laboratory test records that you did not review and evaluate in making batch release decisions. These records contained uninvestigated, out of specification (OOS) data. You did not include the data described below when calculating test results that you used to release finished product. You also failed to identify, investigate, and determine the significance of the OOS results discussed below until our investigators identified the excluded records during our inspection. a) During the inspection, your management admitted that employees in both of your Quality Control (QC) laboratories had frequently conducted unauthorized "trial" High Performance Liquid Chromatography (HPLC) injections prior to additional injections that were used in the reported test results. Although your management stated that this practice ended in February 2014, FDA investigators discovered evidence that this practice continues. The inspection found that the names assigned to each sequenced injection were often changed during testing, obscuring the traceability of repeated injections. The data from "trial" injections was not reviewed or considered in determining batch quality. For example, 1) For the related substances analysis of (b)(4) USP (b)(4) mg Tablets batch (b)(4) conducted on February 25, 2013, there were three sample injections of vial 1_8, all named "TEST," which were run prior to the reported sample injections. The "TEST" injection data was stored in the "Trial" folder located on a personal computer (PC) with no audit trail linked to the HPLC instrument. During the inspection, the calculations that you performed using the target sample weight showed that the "TEST" injections were OOS ((b)(4) as compared to the specification of NMT (b)(4)) for the highest unknown impurity. The "TEST" injections were not reviewed and evaluated when making the	YES 9/19/14

			batch release decision. 2) For the dissolution analysis of (b)(4) USP (b)(4) mg Capsules batch (b)(4) conducted on July 13, 2013, two sets of six sample preparations each were run on the HPLC system as trial sample injections. The trial injection data was stored in the "Trial" folder located on a PC with no audit trail linked to the HPLC instrument. During the inspection, the calculations that you performed using the target sample weight for three of the injections performed on July 11th, 2013, showed that some of the trial injections produced low dissolution test results (Sample-4 (b)(4)%, Sample-5 (b)(4)%, and Sample-6 (b)(4)%, as compared to the Q-value criteria of NLT (b)(4)% of dissolved active ingredient in 45 minutes). The trial sample injections were not reviewed and evaluated by your firm when making batch release decisions. 3) For the assay analysis of (b)(4) USP (b)(4) mg Capsules ((b)(4) drug product) batch (b)(4) conducted on May 15, 2013, two trial HPLC sample injections were run before the reported sample injections. The trial injection data was stored in the "Trial" folder located on a PC with no audit trail linked to the HPLC instrument. During the inspection, the calculations that you performed showed that one of the extra injections was OOS ((b)(4) %, as compared to the specifications of NLT (b)(4)% and NMT (b)(4)% of label claim). The trial sample injections were not reviewed and evaluated as part of the batch release decision	
9-Jan-15	*Micro Labs Limited* (drug product)	India	**4) HPLC sequence GSTA130522-DS showed (b)(4) single injections, in addition to the sequenced injections, during dissolution testing of (b)(4) Tablets ((b)(4) drug product) submission stability batch (b)(4). Two of the extra single injections were from vial 15, labeled as "STD," indicating that the lab may have injected standard solution and not the test sample solution. Notably, the vial 15 contents were then injected a third time and used as the "Sample 6" test result.**	YES 9/19/14

			The trial sample injections were not reviewed when assessing batch quality and product stability. 5) The audit trail for the dissolution analysis of the 9-month long-term stability sample of (b)(4) USP (b)(4) mg Tablets batch (b)(4) conducted on March 22, 2014, showed a single manual injection that was not included in the official test results package. A manual "trial" sample injection from vial position (b)(4) at 12:29 pm was injected between the Set (b)(4) and Set (b)(4) analytical sequences. No deviation was documented regarding the extra sample injection. In addition, the original injection data obtained for vial position (b)(4) was overwritten and not saved. Because the original data was overwritten, you did not review and evaluate it as part of your batch release decision. Examples (1) through (5) are examples of unreported extra data that FDA investigators observed on the analytical systems in your QC laboratories. The inspection also identified (b)(4) unexplained extra HPLC sample injections for the four stability batches that define the stability characteristics of your (b)(4) formulation. b) The inspection also found similar unreported and unexplained sample data acquired during your gas chromatography (GC), ultra violet (UV) spectroscopy and (b)(4) analyses. The extra GC data was stored in the "Trial" folder located on a PC with no audit trail linked to the GC instrumentation. The extra UV and (b)(4) data was stored on the instrument hard drives. This unreported and unexplained data was not reviewed when assessing batch quality and making product disposition decisions. For example, 1) For the (b)(4) analysis of the 9-month long-term stability sample of (b)(4) USP (b)(4) mg Capsules ((b)(4) drug product) batch (b)(4) conducted on January 10, 2014, three extra analyses that were run prior to the reported sample were found on the instrument hard drive. During the inspection, the calculations that you performed showed that two of the extra analyses were OOS ((b)(4)% & (b)(4)%, as compared to the specification of NMT (b)(4)%). Notably, there were no test sample weight records for the three extra (b)(4)	

			tests. The extra sample data was not reviewed when assessing batch quality and product stability. 2) For the dissolution analysis of (b)(4) USP (b)(4) mg Tablets batch (b)(4) conducted on February 21, 2013, a set of test samples was run 14 minutes prior to the reported test samples. The extra data, named slightly differently than the reported test results, revealed several low dissolution test results ((b)(4)%, and (b)(4)%, as compared to the Q-value criteria of NLT (b)(4)% of dissolved active ingredient in 45 minutes). This trial sample data was not reviewed and evaluated when making the batch disposition decision. Your response states that you have initiated investigations into such extra data, together with data integrity audits. We note that your response does not address the testing you have performed on active pharmaceutical ingredients, in-process goods, and validation samples tested by your QC laboratories. Please address these other drugs in your response to this letter. In addition, your response does not include a complete review of all "trial" data (including samples and standards) generated by your firm to ensure that all of the OOS results have been identified and investigated. As part of your response discussed below under "Summary," please include the results of such a review, including steps taken to fully understand the scope and significance of this practice.	
9-Jan-15	*Micro Labs Limited* (drug product)	India	**1. Your firm failed to record and justify any deviations from required laboratory control mechanisms (21 CFR 211.160(a)).** According to your management, a new standard operating procedure (SOP) was approved in February 2014, in order to eliminate your "trial" sample injection practices. However, during our inspection, we observed that your analysts continued these "trial" injection practices after the approval of your new SOP, and that your quality system and your management failed to detect and correct these deviations from the new procedure (see, e.g., Example 1(a)(5) above).	YES 9/19/14

9-Jan-15	*Micro Labs Limited* (drug product)	India	**2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).** FDA investigators discovered a lack of basic laboratory controls to prevent changes to electronically stored data. The following examples show that you lack effective control of the integrity of instrument output data: a) The ten Shimadzu HPLC instruments in the QC "commercial" laboratory were configured to send acquired injection data to PCs without audit trails. b) There was a lack of controls to prevent substitution or overwriting of data. The (b)(4) audit trail dated January 6, 2014, for HPLC MLG/QC/12/026 and the (b)(4) audit trail dated January 15, 2014, for HPLCs MLG/QC/12/031 and MLG/QC/12/027 each showed sample injections marked with the same small graphic symbol. For each of these entries, you replaced the original injection sequence data with data from a single manual injection and failed to save the original sequence data. In your response to this letter, include a chronology of Chromeleon audit trail information that shows all single manual sample injections that replaced data collected during HPLC testing. c) A "File Note" dated February 10, 2014, signed by the QC Head, established that the printed data used for batch disposition decisions from the Metrohm Titrando Instrument MLG/QC/12/048 hard drive was not necessarily the complete data for a batch. Our inspection found that data on the instrument was selected for use and was not protected from change and deletion. Notably, the audit trail capability of this QC "commercial" laboratory instrument was not enabled, even after creation of the "File Note."	YES 9/19/14
9-Jan-15	*Micro Labs Limited* (drug product)	India	**Summary** The above examples are of serious CGMP deficiencies and violations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated and available at your facility to support the safety, effectiveness, and quality of the drug products you	YES 9/19/14

			manufacture. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to assist you with coming into compliance with CGMP regulations and statutory authorities. In your response to this letter, provide the following to the Agency: 1. A comprehensive investigation and evaluation, including a description of the methodology for such investigation and evaluation, of the extent of deficiencies relating to record control, contemporaneous recording, deletion of data, and any other data integrity deficiencies at your firm, such as those identified above; 2. A risk assessment of the potential effect of the observed deficiencies on the quality of your drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug products released for distribution; and 3. A management strategy for your firm that includes a detailed global corrective action and preventive action plan. a) As part of your corrective action and preventive action plan, describe the corrective actions you will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the products manufactured under the violative conditions discussed above. b) In addition, as part of your corrective action and preventive action plan, describe the preventive actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity	
30-Jan-15	*Apotex Research Private Limited* (drug product)	India	**1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).** The inspection of your facility documented multiple incidents of performing "trial" testing of samples, disregarding test results, and reporting only those results from additional tests conducted. For example, a. The official release data for (b)(4) and (b)(4) Tablets (b)(4) mg batch (b)(4) for unknown impurities was reported to be within specification (NMT (b)(4)%).	YES 9/22/14

	483 available		However, the chromatographic data showed that the "trial" injection data for this batch failed the unknown impurities specification with a result of (b)(4)%. b. The official High Performance Liquid Chromatography (HPLC) impurity data for (b)(4) mg Tablets batch (b)(4) ((b)(4)), 3-month stability time-point @ 25oC/60% RH only included the most favorable result obtained from multiple test results without any justification. The data from this batch was submitted to the U.S. FDA as an exhibit batch. In addition to the examples above, our inspection found that 2,803 of 44,643 injection results were not processed or reported in the official data folder for dissolution analysis via HPLC for (b)(4) Tablets. Our inspection identified numerous examples of "trial" injections for various drug products (U.S. and non-U.S. markets), which suggests that this is a common practice. Your response to our findings of "trial" injections attempts to explain the rationale for retesting (b)(4) and (b)(4) (1a above). You state that "the unknown were intermittent spikes resulting in aberrant chromatography caused by electronic disturbance or pressure fluctuation." Your subsequent investigation into the observation concluded that "the unknown impurity peak…is not characteristic of the product and was not observed in the analysis of all commercial and exhibit batches." The fact that you did not observe the peak in commercial and exhibit batches does not justify disregarding the test run or failing to follow up with appropriate corrective actions and preventive actions. According to your response, your laboratory supervisor confirmed that he was aware of the repeated testing of the (b)(4) stability samples (1b above) and that he allowed the analyst to repeat the analysis without conducting further investigation. Your response also states the following: "sample injections were not processed as the analyst failed to record the sample preparations in the analytical laboratory notebook and did not integrate the chromatograms for reporting." This explanation does not resolve the Agency's concerns, but instead raises further issues. You indicate in your response that you initiated investigations for these incidents, some of which occurred over two (2) years ago; however, you did	

			not provide documentary evidence to support your assertions about the repeat testing and related activities. Your response is inadequate because you did not extend the scope of the investigation to the other electronic systems used in each of your laboratories. As part of your corrective action and preventive action plan, address how your firm intends to ensure the reliability and completeness of all analytical data generated at your facility.	
30-Jan-15	*Apotex Research Private Limited* (drug product)	India	**2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).** QC personnel created unauthorized folders on laboratory computerized systems without appropriate oversight. Our review of the HPLC Empower III data collected in 2013-2014 in the commercial QC laboratory found a data folder entitled "WASH." According to your management, the folder was intended for column wash injections using blank solvent prior to and following sample runs, although you have no standard operating procedure (SOP) detailing this process. One of your laboratory analysts stated that this folder does not contain any standard or sample injection results. However, our investigator found that this folder contained a total of 3,353 injection results, some of which appeared to be samples. Your analyst confirmed that the single injection titled "19" in the "WASH" folder represented a trial sample injection performed prior to the official analysis of (b)(4) Tablets on December 19, 2013. From this chromatogram in the "WASH" folder, our investigator documented an unidentified impurity at relative retention time (RRT) (b)(4) calculated at a concentration of (b)(4)%. However, the specification for any unidentified impurity is (b)(4)%. You neither investigated nor reported this out-of-specification (OOS) result. Your firm acknowledged that the analysts involved in performing single injections failed to follow good laboratory practices described in the SOP "General Laboratory Working," and that the analysts conducting the injections in question made decisions to perform unauthorized, unapproved injections. Your response indicates that, during an interview of the laboratory analyst conducted approximately six months after the incident, you determined that he	YES 9/22/14

			may inadvertently have used an old sample vial from the LC tray for the single injection made for the purpose of a column wash. We question your conclusion about the likely cause without having any supporting documentation or record, and based only on memory of what may have happened six months earlier. In correspondence with the Agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the CGMP violations found during the inspection. In addition, FDA's inspection did not include observations related to deletion of specific files, intentionally or otherwise. Rather, FDA's concern pertains to the practice of disregarding failing results, conducting trial injections and retesting products without any investigation. We are also concerned that you do not have documentation to support your decision to retest samples of lots that had initially failed to meet specifications, and you allowed manufacturing activities to occur without the oversight of your quality unit. As part of your comprehensive evaluation and risk assessment, include a detailed description of all computerized systems in your facility used for testing drugs. This description should include information on each electronic folder that was not created pursuant to a valid SOP and an assessment of every file in each such folder, including information about the sample (product), date of test, lot number and original test result over the last five (5) years, except for data relating to exhibit batches, in which case there is no time limitation. Also provide specific information about all retests during these time frames, where an initial out-of-specification or out-of-trend result was disregarded without an investigation and the date on which you became aware such information had been disregarded. In addition, for each batch, provide the number of injections performed and chromatograms reviewed, and of those, the number that were used to generate a reported result. Furthermore, provide an updated assessment on the possible effects of your firm's practices on the quality, safety, and efficacy of the drugs you manufacture or plan to manufacture, including drugs covered by approved or pending applications.	

			In your corrective action and preventive action plan, describe in detail your revised control process for ensuring that batches with retest results are not released until a thorough investigation is conducted. Also describe how you intend to prevent these failures from recurring in the future, and how you will measure the effectiveness of your corrections. Also describe the procedures established to manage and retain all computerized data.	
30-Jan-15	*Apotex Research Private Limited* (drug product)	India	**4. Your firm failed to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)) and your quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192).** For example: Your procedure titled "Quality Unit Responsibility" (#GPOL-004 dated 07/09/2013) states that "any deviation shall be investigated to discover possible causes and prevent possible reoccurrence." Although your written procedure clearly describes the protocols for handling deviations, your quality unit management indicated to our investigator that there were no deviation reports, no OOS investigations, nor any evaluations to address the possible root cause(s) of the deviations/OOSs. Among other failures, your quality unit did not follow your procedures for conducting investigations into the examples listed in citation #1 of this letter. Your firm's implementation of the audit program described in the Global Policy "Audit Program" document #GPOL-015 dated September 7, 2013 is inadequate in that it failed to prevent the recurrence of testing unofficial samples of drug product prior to testing the official sample and generating only those results to be reported. In addition the inspection revealed that failing or otherwise atypical results were not investigated, nor included in the official laboratory control records as required by 21 CFR 211.192. We reiterate that an investigation is necessary for any out-of- specification (OOS) event. Refer to the FDA's guidance on OOS investigations Guidance for Industry, Investigating Out-of-Specification (OOS), Test Results for Pharmaceutical Production. Your quality unit is responsible for assuring that your firm is operating in a	YES 9/22/2014

			sustainable state of control throughout the manufacture and lifecycle of all drugs produced at your facility. Your quality unit has the overall responsibility for oversight and approval of quality related activities. As part of your corrective action and preventive action plan, please describe how your quality unit will provide consistent, adequate review and approval of investigations and production batch records. Be aware that Apotex was notified of our concerns with the practice of "trial" injections during FDA's January 2014 inspection at your Apotex Pharmachem India Pvt. Ltd. located at Plot # 1A Bommasandra Ind. Area, 4th Phase, Jigani Link Road, Bangalore, India. However, our findings during this inspection suggest that corrective actions were not implemented globally. Furthermore, inadequate oversight by your firm's site specific quality units is a repeat finding from WL: 320-10-003 dated March 29, 2010. The need for appropriate and global quality oversight was communicated to Apotex senior management during the regulatory meetings held September 11, 2009, March 31, 2010, and April 11, 2014.	
30-Jan-15	*Apotex Research Private Limited* (drug product)	India	**3. Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile (21 CFR 211.113(a)).** On June 23, 2014, during the inspection of the QC Microbiology Laboratory, our investigators observed missing in-progress microbiological test plates for various finished drug products, in-process products, water, and media growth promotion samples. For example: Finished drug product (b)(4) Tablets (b)(4)mg batches (b)(4) and (b)(4) microbial sample plates/tubes were placed in the incubators on June 19-20, 2014, as documented in your LIMS computer system. The plates should have been incubated for (b)(4) days, per your procedures. On June 23, 2014, no plates/tubes for this batch were observed in any of the incubation chambers. Finished drug product (b)(4) Tablets (b)(4) mg Exhibit Batch (b)(4) sample for microbial testing was prepared on June 13, 2014. Your firm failed to provide the FDA investigator with the worksheet to document the incubation times and media used for the analysis. Your analyst described that the entire microbial	YES 9/22/14

			test for this batch had already been completed the previous week but that the analyst had "forgotten" to document the details on the worksheet. The FDA investigator noted other instances of missing samples/plates for in-process drug products, potable water, and growth promotion, even though records indicated that they were in the incubator. As a result of the above observation, your firm initiated an investigation and reported that 290 (b)(4) plates and 36 media tubes under testing were missing, affecting 45 product sample batches, 12 growth promotion test batches, and 37 negative control plates. Your firm also found discrepancies between the documentation and location of samples/plates and you indicated that the majority of the missing plates were found in the decontamination area for disposal. In your response, you refer to an investigation and indicate that "…two analysts momentarily panicked (upon (1) learning that FDA Investigators were approaching the microbiology Lab and (2) seeing used petri plates from the weekend scattered throughout the laboratory)[sic] and directed the lab technician to immediately remove the petri plates from the microbiology lab … in an utterly misguided and ill-conceived attempt to clean up the microbiology lab prior to the start of the FDA inspection." Your response lacks a comprehensive risk assessment of your failure to follow procedures, your inadequate documentation system and your inadequate practices related to microbiological control. Your response failed to evaluate the effect of these violations on product quality, and did not include an assessment as to whether any other batches have been compromised. ARPL's inability to prevent and detect poor recordkeeping practices raises serious concerns regarding the quality system in place at the time of the inspection. Appropriate controls are essential to assure that the information used for making decisions is trustworthy, accurate, and reliable.	
30-Jan-15	*Apotex Research*	India	**Conclusion** The foregoing examples are of serious CGMP violations demonstrating that your quality system does not adequately ensure the accuracy and integrity of	YES 9/22/14

	Private Limited (drug product)		the data generated at your facility to ensure the safety, effectiveness, and quality of the drug products you manufacture. We found that your quality system failed to ensure the adequate investigation and resolution of quality failures. ARPL failed to investigate OOS results, failed to contemporaneously document failures and report failures, and selected only passing results without the oversight of a quality unit. In your response and in subsequent communications with the agency, you indicated that you interviewed employees and found no evidence of data manipulation or deletion. In focusing on the issues of deletion and alteration of data, you have not sufficiently addressed or resolved other substantial CGMP issues as discussed above. In response to this letter and including the specific requests noted above, provide the following to the Agency: 1. A comprehensive evaluation of the extent of the inaccuracy of recorded and reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above; 2. A risk assessment of the potential effect of the observed failures on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution; and 3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. a) As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the product manufactured under the violative conditions discussed above. b) In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to	

			prevent the recurrence of CGMP violations, including breaches of data integrity.	
27-Feb-15	*Novacyl (Thailand) Ltd* (API) *483 available*	Thailand	**3. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.** The inadequate controls over access to your data raise questions about the authenticity and reliability of your data and the quality of the APIs you produce. Specifically, a. Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory's raw electronic data. Your HPLC computer software lacked active audit trail functions to record changes to analytical methods, including information on original methodology, the identity of the person making the change, and the date of the change. In addition, your laboratory systems did not have access controls to prevent deletion or alteration of raw data. During the inspection, your analysts demonstrated that they were given inappropriate user permissions to delete HPLC data files. b. Moreover, the gas chromatograph (GC) computer software lacked password protection allowing uncontrolled full access to all employees. Your response states that you commit to upgrading your HPLC systems to have audit trails and your GC system to have password protection by July 31, 2014. However, your response lacks sufficient detail of the systems and controls you will implement. Simply turning on audit trail functions is inadequate. In addition, you failed to review historical data to ensure the quality of your products distributed to the US market. In response to this letter, provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computerized systems during the manufacture and testing of your drugs. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacturing and testing that generates electronic raw data. Your response should also describe the controls and procedures you will implement to retain and archive the raw data you generate.	NO
31-Mar-15	*Hospira Spa*	Italy	**3. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute**	NO

	(drug product) *483 available*		**changes in master production and control records, or other records (21 CFR 211.68(b)).** Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition software, TotalChrom®, did not have sufficient controls to prevent the deletion or alteration of raw data files. During the inspection, the investigator observed that the server that maintains electronic raw data for HPLC and GC analyses (the J drive) contains a folder named "Test," and that chromatographic methods, sequences, and injection data saved into this folder can be deleted by analysts. The investigator also found that data files initially created and stored in the "Test" folder had been deleted, and that back-up files are overwritten (b)(4). In addition, because no audit trail function was enabled for the "Test" folder, your firm was unable to verify what types of injections were made, who made them, or the date or time of deletion. The use of audit trails for computerized analytical instrumentation is essential to ensure the integrity and reliability of the electronic data generated. Your response indicates that you have added computer controls to prevent the deletion of folders and files in the J drive for electronic raw data. However, you provide no evidence demonstrating how your firm will prevent deletion of newly created folders and files in each of your computer systems. We acknowledge your commitment to hire a third party consultant to address the inadequacies of your data systems. However, your response is inadequate as it fails to address how you will enable and review audit trail functions for all of your analytical computer systems. In response to this letter, provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computer systems used to support the manufacture and testing of drug products. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacture that generates electronic raw data, as well as for your laboratories. We identified a similar inspectional finding during the December 2013	

			inspection of your Irugattukottai, Sriperumburdur, India, manufacturing facility and noted this finding in an Untitled Letter, issued April 16, 2014. Explain how your firm will implement global corrective actions and preventive actions concerning computer controls and provide a timeline for implementation.	
31-Mar-15	*Hospira Spa* (drug product)	Italy	**4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21CFR 211.194(a)).** Our investigators identified your practice of performing trial sample injections for HPLC analyses. For example, trial injections of (b)(4) stability samples (lot (b)(4) and (b)(4)) were acquired in the "Test" folder prior to official testing. Immediately after the trial injections were completed, the official samples were analyzed. The trial injection raw data, captured in the back-up files, were deleted from the test folder. You retested analytical samples without reporting original results in laboratory records. Because of this practice, you are unable to assure that all raw data generated is included and evaluated when you review analytical test results to determine whether your products conform with their established specifications and standards. For example, (b)(4) lot #(b)(4) failed the content uniformity test, where sample #8 of (b)(4) resulted with a value (b)(4)%. Your firm proceeded to retest the sample on a different instrument without initiating an out-of-specification (OOS) investigation, as required by your chemistry laboratory investigation standard operating procedure, SOP QAG-097. These injections were not reported as part of the original data or included in your laboratory investigation report. Subsequently, the electronic raw data files were deleted. Moreover, there is no procedure describing the use of re-injections for standards or samples on a different system to verify an original result. Your response indicates that the "Test" folders were used to equilibrate the analytical columns and to determine when the system was ready for analysis. It is your responsibility to follow validated methods that include specific procedures to assess the suitability of your instruments. Neither the ICH document Q2R, "Validation of Analytical Procedure: Text and Methodology,"	NO

			nor the United States Pharmacopoeia (USP), General Chapter <1058>, "Analytical Instrument Qualification," provides for use of “trial” injections as part of a validated method. Your rationale that you retested failing samples on different analytical instrumentation to evaluate system suitability is inadequate. See USP General Chapter <621>, “Chromatography,” which discusses system suitability tests and the use of replicate injections of a standard preparation or other standards to determine if the requirements for precision are satisfied. These are serious CGMP violations that demonstrate that your quality system does not adequately ensure the accuracy and integrity of the data you generate to support the safety, effectiveness, and quality of the drug products you manufacture. We acknowledge your commitment to work with a third party consultant to conduct a comprehensive assessment of your firm’s manufacturing, laboratory, and quality operations. However, it is your responsibility to ensure that the third party audit includes a full evaluation of sophisticated electronic systems and the potential for manipulation of such systems. In response to this letter, provide the following to the Agency: 1. A comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above; 2. A risk assessment regarding the potential effect on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution; and 3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. a. As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the product manufactured under the violative conditions discussed above.	

			b. In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity. The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.	
6-Apr-15	*Yunnan Hande Bio-Tech Co. Ltd.* (API)	China	**1. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.** You lacked controls to prevent the unauthorized manipulation of your laboratory's electronic raw data. Specifically, your infrared (IR) spectrometer did not have access controls to prevent deletion or alteration of raw data. Furthermore, the computer software for this equipment lacked active audit trail functions to record changes to data, including information on original results, the identity of the person making the change, and the date of the change. Audit trails that capture such critical data about the quality of your batch production should be reviewed as part of the batch review and release process. We acknowledge your commitment to upgrade the IR software by adding full audit trail capabilities in compliance with CGMP. In your response, you also commit to obtain information about the (b)(4) archival of all data obtained on laboratory computerized systems, and to evaluate software upgrades to other instrumentation. However, your response is inadequate because you have not specified how you will ensure the integrity of raw analytical data or maintain data before you complete your planned corrective actions and preventive (CAPA) actions. In response to this letter, provide your comprehensive CAPA plan for ensuring that electronic data generated in your manufacturing operations, including laboratory testing, cannot be deleted or altered. It essential that your firm	NO

			implement controls that prevent the omission of data, and record information about changes to existing data, such as the date of the change, identity of person who made the change, and an explanation or reason for the change. Any such changes should be made in accordance with an established and appropriate procedure. Your response should address your laboratory equipment and any other manufacturing-related equipment that may be affected by the lack of adequate controls to prevent data manipulation.	
6-Apr-15	*Yunnan Hande Bio-Tech Co. Ltd.* (API)	China	**2. Failure of your quality unit to ensure that materials are appropriately tested and the results are reported.** The inspection documented that an analyst at your firm failed to perform the IR identity test for all lots of (b)(4), API, as part of your quality control release. Instead, the analyst at your firm altered the file name in the spectrophotometer containing the sample identification information for (b)(4) API lot # (b)(4), tested on April 2, 2014, to support the release of two previously manufactured lots, # (b)(4) and (b)(4). In your response dated May 1, 2014, you admit that an analyst altered the identity test result for lot # (b)(4) to approve and release lots # (b)(4) and # (b)(4). This practice is unacceptable and raises serious concerns regarding the integrity and reliability of the laboratory analyses conducted by your firm. Laboratory control records must include accurate and truthful documentation of all raw data generated during each test, including graphs, charts and spectra from laboratory instrumentation. These records must be properly identified and maintained to demonstrate that each API lot was tested and met the release specification before the lot is released. Your response is inadequate because you did not perform a comprehensive investigation and a retrospective review to ascertain the extent of this data alteration practice. A cursory review of records does not ensure that other personnel did not manipulate or inaccurately report test data. The review was also insufficient because you did not review data generated from other computerized systems such as high performance liquid chromatography or gas chromatography to determine if data generated by these systems were also manipulated or altered.	NO

6-Apr-15	*Yunnan Hande Bio-Tech Co. Ltd.* (API)	China	**3. Failure of your quality unit to exercise its responsibility to ensure the APIs manufactured at your facility are in compliance with CGMP, and meet established specifications for quality and purity.** For example, your quality unit failed to detect that your laboratory altered IR raw data and misrepresented the results for approval and release of (b)(4), API lots# (b)(4) and (b)(4). Your response indicates you revised your data review procedure to include the requirement for cross lot comparison review for batches tested during the same period. Additionally, you commit to strengthen work processes to prevent future data manipulation by ensuring the data is traceable and training the reviewers on data tracking. Your response is inadequate in that it does not fully address the failure of your quality unit to detect and prevent the manipulation or alteration of laboratory documents. Additionally, your response is incomplete because you have not provided a comprehensive plan to ensure the integrity of all data used to assess the quality and purity of APIs manufactured at your facility.	NO
6-Apr-15	*Yunnan Hande Bio-Tech Co. Ltd.* (API)	China	[**COMENT**]: The above examples are serious CGMP deviations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated at your facility to support the safety, effectiveness, and quality of the drug products you manufacture. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to assist you with coming into compliance with CGMP requirements. However, it is your responsibility to ensure that any third party audit includes appropriate evaluation of sophisticated electronic systems and the vulnerability to data integrity manipulation of such systems. In response to this letter, provide the following to the Agency: 1. A comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above; 2. A risk assessment regarding the potential effect on the quality of drug products. As part of your risk assessment, determine the effects of your	NO

			deficient documentation practices on the quality of the drug product released for distribution; and 3. A management strategy for your firm that includes the details of your corrective action and preventive action plan. a) As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, monitoring of complaints, and/or other steps to assure the quality of the product manufactured under the violative conditions discussed above. b) In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity. The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations.	
27-May-15	*VUAB Pharma* (API)	Czech Republic	**1. Failure to prevent unauthorized access or changes to data and to provide adequate controls preventing data omissions.** Our inspection noted that your firm did not retain complete raw data from testing performed to assure the quality of (b)(4), API. Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms that form the basis of your product release decisions. Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system, which is intended to demonstrate correct operation of the HPLC. These discrepancies included injection sequences and values to calculate relative standard deviation (RSD). While investigating these discrepancies, our investigator requested the original electronic raw data. Your quality unit, after consulting with the	YES 4/10/15

			Information Technology (IT) department, stated they were unable to retrieve the original electronic raw data because back-up discs were unreadable. Your quality unit then stated that back-up disks have been unreadable since at least 2013. Your HPLC system is used to test (b)(4), API for batch release. However, without complete, accurate, reliable, or retrievable raw data about the HPLC system's qualification, you lacked complete assurance that the system was operating as intended. You also failed to have proper controls in place to prevent unauthorized manipulation of your laboratory's raw electronic data. Our inspection revealed your HPLC system did not have access controls to prevent alteration or deletion of data. Your HPLC software lacked an audit trail recording any changes to the data, including: previous entries, who made changes, and when changes were made. During the inspection, we also noted that all laboratory employees shared a common log-in and password to access the system. This lack of control over the integrity of your data raises questions about your analytical data's authenticity and reliability, and about the quality of your APIs. We note that the September 2008 FDA inspection uncovered concerns over your handling of raw analytical data, including discrepancies between laboratory notebooks and printed chromatograms. Your response states you are qualifying a new HPLC system which allows operator specific passwords and has audit trial and back-up functions. Your response also states you will implement a new electronic back-up system in your QC chemistry department. However, your response lacks sufficient detail about systems and controls you will implement. Simply activating audit trail functions and instituting password controls is inadequate. In addition, you failed to review historical data to ensure the quality of your products distributed to the US market. In your response to this letter, provide a comprehensive corrective action plan for computer system controls over all laboratory and manufacturing instrumentation and equipment. This response should include but not be limited to: • Information regarding changes in the reliability of your information technology infrastructure, including but not limited to improved computer	

			systems, systems validation, revised procedures, and appropriate retraining of employees that will be implemented immediately to ensure your firm creates and retains complete and accurate electronic raw data. • Your firm's procedure for the establishment, issuance, and control of passwords used to access your analytical instrumentation. All access levels for computerized systems should be clearly defined and documented in a written procedure. • A detailed summary of the steps taken to train your personnel on the proper use of computerized systems. The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations.	
8-Jun-15	*Transox Inc.* (drug product, medical gas)	US	**1. For each batch of drug product, your firm must have appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, before release (21 CFR 211.165(a)).** Your firm does not have appropriate documentation. During our inspection of your facility, we documented multiple incidents of inaccurate batch production records containing erroneous statements, including results that were not derived from analytical testing or from your supplier's Certificates of Analysis (CoAs). According to your batch production records, your results were obtained from a "Post Fill Purity Test." The records are labeled "ANALYTICAL RESULTS OBTAINED BY USING THE **(b)(4)** OXYGEN ANALYZER." However, on November 13, 2014, the FDA investigator observed cobwebs between the portable **(b)(4)** Oxygen Analyzer and the adjacent wall. The general manager stated that your firm does not use the **(b)(4)** Oxygen Analyzer, which directly contradicts your batch production records.	N/A

			Further, on November 13, 2014, our investigator reviewed a number of batch records and asked you why all the analytical results reported on these batch production records were identical. Although your batch production records indicate that analytical results were obtained from the **(b)(4)** Oxygen Analyzer, you responded to the investigator's question by stating that the values were actually obtained from your supplier's CoAs. However, the values reported on multiple batch production records disagree with the CoAs for those lots. a) For instance, the batch production record for your lot 011514 (supplier lot 515244) states your purity test result on the **(b)(4)** Oxygen Analyzer was 99.9%. In contrast, the CoA for supplier lot 515244, dated December 23, 2013, states 99.74% purity. b) Similarly, the batch production record for your lot 032614 (supplier lot 515240) states your purity test result on the **(b)(4)** Oxygen Analyzer was 99.9%. In contrast, the CoA for supplier lot 515240, dated March 20, 2014, states 99.84% purity. In your response, you stated that you have created a Policy and Procedure Manual, which includes Batch Production and Control Records and an Equipment Calibration Schedule. However, your response does not include any retrospective reconciliation of batch production records and CoAs, or testing of lots currently in stock or in distribution. Retrospective assessment is essential to determining if batches released prior to your implementation of new procedures met purity specifications.	
8-Jun-15	*Transox Inc* (drug product, medical gas)	US	**Conclusion** These examples are serious CGMP violations. Your quality system does not adequately ensure the accuracy and integrity of the data generated at your facility to support the safety, effectiveness, and quality of the drug products you manufacture. We strongly recommend that you hire a qualified third party auditor/consultant to help you come into compliance with CGMP regulations and statutory requirements.	N/A

			As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers; recalling product; conducting additional testing; enhancing systems for monitoring, investigating, and responding to deviations, complaints, and returns; and/or other steps, to assure the quality of the product manufactured under the violative conditions discussed above. In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take to prevent recurring CGMP violations. These may include revising procedures, implementing new controls, training or re-training personnel, and/or other steps.	
13-Jul-15	*Mahendra Chemicals* (API)	India	**2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.** Your laboratory systems lacked access controls to prevent raw data from being deleted or altered. For example, a) There is no assurance that you maintain complete electronic raw data for your Gas Chromatography (GC) instrument. FDA investigators observed multiple copies of raw data files in the recycle bin connected to the GC instrument QC-04 even in the presence of "Do Not Delete Any Data" notes posted on two laboratory workstation computer monitors. b) Employees were allowed uncontrolled access to operating systems and data acquisition software tracking residual solvent, and test and moisture content. Our investigators noted that there was no password functionality to log into the operating system or the data acquisition software for the GC, the High Performance Liquid Chromatography (HPLC) instrument QC-17, or the Karl Fischer (KF) Titrator QC-13. C) HPLC SpinChrome and GC Lab Station data acquisition software lacked active audit trail functions to record changes in data, including original results, who made changes, and when.	NO

			In your response, you state that your laboratory GC, HPLC and KF systems are now password-protected and that you have begun drafting analytical software password procedures for the GC, HPLC and KF laboratory instruments. However, your response does not state whether every analyst will have their own user identification and password. You also mention plans to install a validated computer system. However, you did not provide a detailed corrective action and preventive action (CAPA) plan or conduct a review of the reliability of your historical data to ensure the quality of your products distributed to the U.S. market. Inadequate controls of your computerized analytical systems raise questions about the authenticity and reliability of your data and the quality of your APIs. It is essential that your firm implements controls to prevent data omissions or alterations. It is critical that these controls record changes to existing data, such as the individuals making changes, the dates, and the reason for changes. In response to this letter, provide your comprehensive CAPA plan for ensuring that electronic data generated in your manufacturing operations, including laboratory testing, cannot be deleted or altered. Also identify your quality control laboratory equipment and any other manufacturing-related equipment that may be affected by inadequate controls to prevent data manipulation.	
13-Jul-15	*Mahendra Chemicals* (API)	India	**1. Failure to record activities at the time they are performed and destruction of original records.** Specifically, your employees completed batch production records entries days after operations had ended, released lots before the proper approvals, and failed to maintain original manufacturing data for critical steps in the batch production records. For example, Our investigators found that some of your operators used “rough notes” (unbound, uncontrolled loose paper) to capture critical manufacturing data and then destroyed these original records after transcription into the batch production records. For example, the (b)(4) chemist recorded original manufacturing data as rough notes and left these rough notes for the (b)(4) chemist to transcribe into the batch production records. The next morning, the	NO

			(b)(4) chemist signed the batch production records and destroyed the original rough notes. We interviewed employees during the inspection who confirmed your firm's practice of transcribing data to batch records and destroying original records. Additionally, our investigators found backdated batch production records dated February 10 to February 25, 2014, signed by your Production Manager and Technical Director in the "Batch Manufacturing Record Reviewed [sic] by" section. The Technical Director stated that he was not in the facility on these dates and was "countersigning" for another person who allegedly performed these review activities. However, these records did not contain signatures (contemporaneous or otherwise) of the alternate reviewer who purportedly conducted the review. Furthermore, the Technical Director backdated his own signature to the date the quality unit (QU) reviewed and released your drug product. His backdated signatures are on (b)(4) batch records for lots (b)(4); and (b)(4) batch records for lots (b)(4). You released these batches before the Technical Director returned to the facility and backdated his signatures. The batch records, therefore, do not demonstrate that you completed your required review before releasing your products. You did not distribute these lots to the United States. However, your failure to assure proper review of production and control records before product release raises questions about the authenticity and reliability of your data and the quality of the APIs you produce for the U.S. market. Your response does not explain your use of rough notes for documenting CGMP data. This practice, in conjunction with backdating records, raises additional concerns about the integrity, authenticity, and reliability of all your data, and the quality of your APIs. Batch production records must include complete and accurate information on the production and control of each batch. Employees responsible for supervising or checking significant steps in manufacturing operations must do so and appropriately document their review of critical steps (for example, records must not be backdated and signatures must be authentic). In your response to this letter, describe how systems and procedures will be changed to assure that all CGMP operations are documented at the time they	

			occur and that original records are preserved in the batch records. Explain how you will determine that all personnel involved with the preparation and review of API records adhere to your procedures. Also, provide your plans to ensure QU review of completed batch production and laboratory records before API release.	
13-Jul-15	*Mahendra Chemicals* (API)	India	**3. Failure to train employees on their particular operations and related CGMP practices.** a) In interviews, multiple employees stated that they had not received on-the-job training for their production operations. b) There was no record of training for the GC analyst testing for residual solvent release in final API. c) According to your "(b)(4) Training Program" procedure, a report is generated for each training with the names of trainer and trainees, subjects covered, evaluation sheets, etc. However, you were not able to provide any training reports to our investigators. In your response, you state that, per your standard operating procedure (SOP) from 2013, your firm has trained all employees by contracting a consultant. However, as noted in item 3c, our inspection revealed that your firm is not following this procedure. In response to this letter, provide a corrective action plan for investigating the extent of this deficiency. Address why manufacturing and quality management failed to detect these training deficiencies. Include updated procedures and proper quality oversight to ensure that employees are adequately trained to perform all of their responsibilities for consistent manufacturing and laboratory operations. Explain how you will determine the effectiveness of your new consultant trainer, as your previous consultant was permitted to ignore your training procedures. The examples in this letter are serious CGMP deviations. Your quality system does not adequately ensure the accuracy and integrity of data generated at your facility to support the safety effectiveness, and quality of the drug	NO

			products you manufacture. Our current significant findings also indicate that your quality unit is not able to fully exercise its responsibilities. It is essential to give your quality unit appropriate authority and staff to carry out its responsibilities. We strongly recommend hiring a qualified third-party auditor/consultant with experience in detecting data integrity problems to help you comply with CGMP requirements. Note that it remains your responsibility to ensure that any third-party audit evaluates your sophisticated electronic systems and their vulnerability to data integrity manipulation.	
(drug product)	*Mylan Laboratories Limited* (Drug product) *483 available* *483 available* *483 available*	India	**B-3. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel can change master production and control records, or other records (21 CFR 211.68(b)).** Your Siemens computer-based BMS and NVPMS do not require passwords to access the network and servers. Your contractors' access is uncontrolled. Responsibilities for system administrators are undefined. This violation is recurrent. On September 9, 2013, we cited your firm in Warning Letter 320-13-26 for failure to exercise appropriate controls over computer or related systems.	NO
2-Sep-15	*Pan Drugs Limited* (API)	India	**3. Failure to maintain complete data derived from all testing and to ensure conformance with established specifications and standards.** For (b)(4) USP, lot number (b)(4), manufactured in June of 2012, the "ANALYTICAL TESTING PROTOCOL" used to record the results of testing contained fillable sections for heavy metals analysis, residual solvent analysis, the names of analysts performing those tests, and the names of a second person to review the results. The document provided to the investigator for the lot indicated that: a. No heavy metals analysis was performed	YES 5/5/15

			b. The name of the analyst who performed the residual solvents analysis was not included c. No second person reviewed the documents for accuracy, completeness, and compliance with established standards In your response, you provided subsequent test results on lot number (b)(4), and stated that you are retraining personnel involved in analytical testing. You also stated that you "will check all analytical records till current batch and take corrective action for all such types of oversight errors." Your response failed to specify whether any lots were released that lacked complete analytical testing information, either because the test was not performed or the data was not recorded. You also did not indicate if any lot was released without a secondary review of results to ensure compliance with established standards. In response to this letter, please provide a list of all lots distributed to the U.S., within expiry. For each lot, indicate whether the lot was released without complete testing information or secondary review. If, in compiling this data, you find any discrepancies that show material was released that did not comply with established standards, please provide your plan of action for that material. Because of continuing CGMP issues at your firm, we recommend that you engage a third party consultant with appropriate CGMP expertise to comprehensively assess your firm's entire operation, including facility conditions, procedures, processes, laboratory controls, and quality management systems. Your executive management is responsible for the ongoing acceptability of your operation, and for affording proper daily oversight to assure the identity, strength, quality, and purity of the drugs you manufacture.	
2-Sep-15	*Pan Drugs Limited* (API)	India	**Disparity in Information Provided During the Inspection vs. US Import Records** During the July 2014 inspection, you stated that (b)(4) API is the only product your facility manufactures and distributes to the U.S. market. Accordingly, the FDA investigator focused solely on (b)(4) manufacturing operations.	YES 5/5/15

			However, after reviewing import entries, we found that you have been manufacturing and shipping significant quantities of (b)(4) other APIs to the United States. The import documents detail shipments directly from your facility both before and after the inspection of (b)(4), and (b)(4). In your response to this letter, please provide an explanation as to the disparity between the statement you made to the investigator and the importation records for drugs you have shipped to the United States.	
28-Sept-15	*Unimark Remedies Limited* API	India	***1. Failure to document production and analytical testing activities at the time they are performed.*** During our inspection, we found that test results and other entries in the production records were not entered while batches were in production. For example, a. The investigator observed **(b)(4)** batch **(b)(4)** production on March 18, 2014. The start and stop times and **(b)(4)** for Step #**(b)(4)** were not recorded or signed in the batch record contemporaneously. b. For your **(b)(4)** products returned due to the presence of extraneous threads, the investigator found many inconsistencies in your reprocessing batch records. Specifically, operators signed batch records for periods when they were not in your facility, indicating these activities were documented by personnel who did not perform them. During the inspection, and in your written responses, your managers admitted that the batch records were created after the manufacturing process. c. Water testing records for sampling point **(b)(4)** on March 19, 2014, were incomplete. Specifically, the analyst did not record observations at the time they were made on March 18, 2014. Your microbiology records did not identify who prepared the samples, when they began incubation, who read the samples, or when the samples were read.	NO

			According to your responses to these FDA 483 observations, your manufacturing staff did not exhibit acceptable documentation practices, and your chemist or microbiologist each neglected his work. However, your management is responsible for routine oversight of manufacturing and testing operations, including the activities of operators and other personnel, and your responses do not address the failure of management and the flaws in your overall quality system. In response to this letter, conduct and provide the results of a comprehensive investigation into your poor documentation practices. Your investigation should address the flaws in your quality systems and management oversight that led to these serious deficiencies. Provide your plans to revise your procedures so that all CGMP operations are documented at the time they occur. Also provide your plans to revise your procedures so that you preserve original or true copies of data in the batch records. Also provide your procedures for addressing deviations from acceptable documentation practices, including training and oversight of personnel whose duties require preparation and review of API records.	
28-Sept-15	*Unimark remedies Limited* API	India	***2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.*** Your laboratory systems lacked access controls to prevent raw data from being deleted or altered. For example: a. During the inspection, we noted that you had no unique usernames, passwords, or user access levels for analysts on multiple laboratory systems. All laboratory employees were granted full privileges to the computer systems. They could delete or alter chromatograms, methods, integration parameters, and data acquisition date and time stamps. You used data generated by these unprotected and uncontrolled systems to evaluate API quality.	NO

			b. Multiple instruments had no audit trail functions to record data changes. We acknowledge your commitment to take corrective actions and preventive actions to ensure that your laboratory instruments and systems are fully compliant by January 15, 2015. In response to this letter, provide a copy of your system qualification to demonstrate that your electronic data systems prevent deletion and alteration of electronic data. Describe steps you will take (e.g., installing better systems or software) if your qualification efforts determine that the current system infrastructure does not assure adequate data integrity. Explain the archival process your firm has implemented to address these issues and how you will evaluate the effectiveness of these corrections. Provide a detailed summary of the steps taken to train your personnel on the proper use of computerized systems.	
28-Sept-15	*Unimark remedies Limited* API	India	***3. Failure to maintain complete data derived from all testing, and to ensure compliance with established specifications and standards.*** Because you discarded necessary chromatographic information such as integration parameters and injection sequences from test records, you relied on incomplete records to evaluate the quality of your APIs and to determine whether your APIs conformed with established specifications and standards. For example: a. During the inspection, the investigator found no procedures for manual integration or review of electronic and printed analytical data for **(b)(4)** stability samples. Electronic integration parameters were not saved or recorded manually. When the next samples were analyzed, the previous parameters were overwritten during the subsequent analyses. b. We found that some analytical testing data was inadequately maintained and reviewed.	NO

			i. Your HPLC 14 computer files included raw data for undocumented **(b)(4)** stability samples analyzed on December 30, 2013, but no indication of where these samples came from and why they were tested. ii. In a data file folder created on May 22, 2013, 23 chromatograms were identified as stability samples for **(b)(4)** lots **(b)(4)**, and **(b)(4)**. Results were not documented. More importantly, the acquisition date was July 7, 2013, more than six weeks after the samples were run. iii. **(b)(4)** lots **(b)(4)** and **(b)(4)** were not in your stability study records at the time of inspection. Additionally, there were no log notes of any samples from the three lots removed from the stability chamber. You responded that "the probable reason for this inconsistency in data acquisition was due to some malfunction in the computer system at the time of data acquisition." Your response is inadequate because you have provided neither evidence to support this conclusion, nor a retrospective review of the effects your incomplete analytical data records may have had on your evaluation of API quality. In response to this letter, provide your revised procedures and describe steps you have taken to retrain employees to ensure retention of complete electronic raw data for all laboratory instrumentation and equipment. Also, provide a detailed description of the responsibilities of your quality control laboratory management, and quality assurance unit for performing analytical data review and assuring integrity (including reconcilability) of all data generated by your laboratory.	
22-Oct-15	*Sandoz Private Limited* (API)	India	**5. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).** On August 25, 2014, we found there were no access restrictions to laboratory data generated by the (b)(4) instrument used to test and release raw materials	NO

			and in-process drug products. Your laboratory computer systems lack necessary controls to prevent data tampering and to detect data that may have been compromised. We acknowledge that you are in the process of qualifying a new (b)(4) instrument. However, your response is still inadequate; you failed to evaluate the effects of potentially compromised data on release decisions that rely on data generated by this uncontrolled system. These examples are serious CGMP deficiencies and violations. They demonstrate that your quality system does not adequately ensure the accuracy and integrity of data generated and available at your facility. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to help you come into compliance with CGMP regulations and statutory authorities. In your response to this letter, provide the following: A comprehensive investigation and evaluation. Describe your methodology. Results should include conclusions about the extent of data integrity deficiencies and their root causes, which may involve record control, contemporaneous recording, deletion of data, and other data integrity deficiencies. A risk assessment of how the observed deficiencies may affect the reliability and completeness of quality information available for your drug products. Also determine the consequences of your deficient documentation practices on the quality of drug products released for distribution. A management strategy that includes a detailed global corrective action and preventive action plan. Describe the corrective actions you will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring complaints, or other steps to assure the quality of your products manufactured under the violative	

			conditions discussed above. Describe the preventive actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.	
5-Nov-15	*Dr. Reddys Laboratories Limited* (API and drug product) *483 available* *483 available*	India	**3. Failure to record activities at the time they are performed.** Your employees did not complete batch production and control records immediately after activities were performed. When QA reviewers noticed missing entries in the batch records, they made a list of all the missing items on separate, uncontrolled pieces of paper that were provided to the production manager. Data were later entered into CGMP documents after operations had already ended as though they had been entered at the time of the operation. For example, on November 17, 2014, we saw eight production records for (b)(4) and (b)(4) that had blank entries for weights of material used for production, checked-by signatures, accessories used, in-house batch numbers, quantity added, and product labeling for material dried specimens. The yield report sheet and batch summary sheet were also incomplete. Missing information was recorded on uncontrolled sheets of paper instead of in your official records. Your staff told us that they write on sheets of paper to make management aware of missing data in the batch record. Your December 15, 2014 response to this finding stated, "[w]e acknowledge and regret that some of the data such as weights, checked by signature etc…were not entered" (sic). You claim this practice was only observed in records related to the manufacture of (b)(4) active ingredients, and that the missing entries for weights were due to manufacturing equipment inadequacies. These explanations do not justify your use of uncontrolled paper for documenting CGMP-relevant data, nor do they justify your failure to document events and information contemporaneously. For example, it is unacceptable to use uncontrolled sheets of paper to document deviations from the manufacturing process, regardless of whether such deviations are critical or	NO

			non-critical. Even non-critical deviations from established procedures should be documented and explained, and reviewed and approved by your quality unit prior to the release of your intermediates or APIs. In response to this letter, provide an assessment of the effects of your poor documentation practices on the quality of other batches produced in your facility. Specify when you discontinued using unofficial paper records, how you will prevent this practice from reoccurring, and the controls you are implementing to ensure that all CGMP-related operations are documented as they occur.	
5-Nov-15	*Dr. Reddys Laboratories Limited* (API and drug product)	India	**3. Failure to prevent unauthorized access or changes to data.** During the inspection, we found that QC laboratory analysts were authorized to release finished product in your firm's computerized SAP inventory management system. Release or rejection of finished product is a non-delegable responsibility of the quality unit, and cannot be shared with laboratory analysts or other personnel. However, your SAP system permitted QC laboratory analysts to release intermediates from one process to the next process, as well as to release finished product into the market without requiring quality unit oversight. In your February 19, 2015 response, you acknowledged that your SAP system permitted QC laboratory analysts to release intermediates and APIs, including release of finished API for distribution. However, you claimed that QC did not actually release finished API for commercial distribution using SAP because your quality unit is bound by SOP #01-021, "QA Release," which provides for quality unit oversight. You also stated that you had "unambiguously verified that not a single commercial API batch has been released by QC alone" (sic) within the timeframe of January to December 2014. You acknowledged the need to build additional controls into your SAP system, and committed to amend the SAP configuration and stop solely relying on the SOP as the control tool. You also committed to review all batches manufactured and distributed from the site to determine if any products had been released for commercial distribution by QC alone. On May 21, 2015, you reported that three batches of an API (not identified in	NO

			your correspondence) were released for commercial distribution by a QC analyst in 2013. You concluded that this was an isolated incident. In subsequent correspondence dated September 14, 2015, you stated that allowing QC analysts to release batches of intermediates was a deliberate part of Dr. Reddy's control strategy: this "functionality in SAP was given to QC personnel to allow the release of intermediates only for internal use in additional processing without QA intervention." You reiterated that your review of the release process over two years indicated that "the process operated as intended with no deviations," even though you had just reported such a deviation to the FDA in your May 2015 correspondence. In your response to this letter, explain the discrepancy between your May 2015 report regarding release of API by a QC analyst and your September 2015 assertion that no such deviations had transpired over the course of two years. Describe the improvements made to the configuration of your SAP system, including controls to limit analyst functions and specifically to prevent QC analysts from releasing finished API or intermediates for commercial distribution. Explain further how your SAP system has been re-configured to reflect the quality unit's oversight of QC decisions to release intermediate for further use. Finally, show how your SOP on commercial release is aligned with the configuration and functionality of your SAP system.	
5-Nov-15	*Dr. Reddys Laboratories Limited* (API and drug product)	India	**2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.** During the inspection we found the following examples of uncontrolled access to electronic systems used to generate data in your Product Development Laboratory (PD Lab). a. Your HPLC systems are configured so that no passwords are required to log in. Credentials are unverified. Anyone who accesses the system can use software administrator privileges, which means that there is no electronic or procedural control to prevent manipulation of data. b. Your HPLC system had no access controls to prevent alteration or deletion	NO

			of data. Furthermore, your HPLC software lacked an audit trail feature to document all activities related to the chromatographic analysis. Because of this failure, neither your quality unit nor your laboratory staff could demonstrate that HPLC records included complete and unaltered data. They were also unable to verify that there had been no alterations or deletions. c. One of your analysts stated that another, unknown individual had logged into the system using the analyst's credentials. This unknown individual performed injections and deletions without the analyst's knowledge. According to your December 15, 2014 response, you used the equipment and systems in the PD Lab to conduct non-CGMP activities, which you characterize as "extended" investigations to identify impurities in APIs and intermediates, improve processes, qualify sources of key starting materials, and conduct laboratory experiments to address Drug Master File (DMF) deficiencies. Your response is inadequate, because many of these activities are subject to CGMP. Additionally, you based final disposition decisions on uncontrolled investigations conducted in the PD Lab. In your response to this letter, explain how you will ensure that all analyses performed in support of product disposition decisions and other CGMP activities will be reviewed, approved, and overseen by your quality unit. Provide specific details of the steps you have taken to prevent unauthorized access to your electronic data systems and to ensure that data systems retain complete, accurate, reliable, and traceable results of analyses performed.	
17-Dec-15	*Sun Pharmaceutical Industries Ltd.* (drug product)	India	**6. Your firm failed to establish appropriate controls over computers and related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211. 68(b)) You lacked audit trails or other sufficient controls to facilitate traceability of the individuals who access each of the programmable logic controller (PLC) levels or Man-Machine Interface (MMI) equipment. You had no way to verify that individuals have not changed, adjusted, or modified equipment operation parameters.** Access to production equipment used in parenteral manufacturing and solid (b)(4) dosage forms used a password shared by four or five individuals to gain access to each individual piece of equipment and access level. During our	NO

	483 available		inspection, your Executive Production and QA manager confirmed that the password was shared. Neither your operators nor your supervisors had individual passwords. During our inspection, firm officials also confirmed that you had not established or documented a control program to describe the roles and responsibilities of production equipment system administrators. There was also no record documenting the individuals who have access to the production equipment or the manner in which individual personnel access production equipment. In your response, you indicated that you have performed a comprehensive review of the PLCs and manufacturing equipment associated with the production of parenteral and solid (b)(4) dosage forms to assess your access controls and traceability to individual operators. You suggested that traceability to the individual operator could be determined through a hybrid system using the batch manufacturing record and equipment logbook. However, because you used shared login credentials that did not permit identification of a specific person using the shared login, you have not shown how your hybrid system could link specific actions to a specific operator. In your response, you also stated that you will conduct a retrospective risk assessment to evaluate the effects of your deficient computerized system controls on the quality of the products manufactured using this automated equipment. However, you did not indicate the timeframe for your review, your criteria for evaluating the effects of these deficiencies on your products, or any actions needed for products within expiry. Finally, in your response, you indicated that you planned to (b)(4). Your response is inadequate because you did not indicate what controls you will implement in the interim to assure that only authorized personnel change your production or other records. In response to the letter, provide your retrospective review and risk assessment of lots manufactured using equipment with shared passwords. Explain how you will identify which operators or personnel performed and recorded specific activities, your criteria for evaluating how manufacturing and	

			quality of your products has been affected by your deficient controls, and any actions needed to assure the quality, safety, and efficacy of products within expiry.	
23 Dec 2015	*Cadila Healthcare* (API and drug product) *483 available* *483 available*	India	**B. Cadila Healthcare Limited India (Zyfine) (FEI 3006595385)** **2. Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.** a. Your firm failed to adequately control the use of computerized systems in the quality control laboratory. Our inspection team found that the laboratory manager had the ability to delete data from the Karl Fischer Tiamo software. During our limited review of your Karl Fischer data, we found that one file had been deleted. However, because the audit trail function for the Karl Fischer Tiamo software was not activated, and because eight different analysts share a single username and password, you were unable to demonstrate who performed each operation on this instrument system. You do not have a record of the acquisition of all data, nor do you have records of changes to or modifications of such data. b. The inspection also found that a file containing the moisture content results for **(b)(4)** API batch **(b)(4)** had been deleted. This deletion was not identified and reviewed as part of your batch release decision. In your response, you indicated that the batch was within specifications according to raw data retrieved from the laboratory notebook. However, your response failed to address the deleted electronic record. You also did not indicate whether this deletion was an isolated incident or if other QC laboratory instruments and systems are configured to permit deletion of data. In response to this letter, provide a comprehensive corrective action plan addressing the foregoing concerns. Include information regarding revised procedures, system upgrades, controls you have implemented, and appropriate retraining of employees to ensure that data generated and maintained on computerized systems is protected against unauthorized manipulation and deletion.	NO
23 Dec 2015	*Cadila Healthcare*	India	**B. Cadila Healthcare Limited India (Zyfine) (FEI 3006595385)**	NO

			3. Your firm failed to ensure that all quality-related activities are recorded at the time they are performed. Our inspection found that your firm's employees use "rough or unofficial notebooks" to document various CGMP activities. During their walk-through, our investigators found "unofficial" notebooks in the engineering office at your Zyfine **(b)(4)** plant, in the quality assurance office at your Zyfine **(b)(4)** plant, and in the scrap yard shared by **(b)(4)** plants. a. For example, an "unofficial" notebook found in the engineering office stated, "Pseudomonas present in **(b)(4)** water system" on November 26, 2014 and "**(b)(4)** water system (Activity) investigation" on November 25, 2014. Your firm was unable to provide the investigators with any documentation regarding *Pseudomonas sp.* found in your water system and the related investigation. In your response to the observation, you explained that this failure occurred during qualification of your water system, which was still in progress at the time of your response. Your response was deficient; the fact that your investigation into the presence of *Pseudomonas sp.* in your water system transpired during the qualification of that system is irrelevant. You must document all CGMP activities at the time you perform them, including equipment qualification and any deviations observed during such activities. b. Our investigators found several plastic bags filled with paperwork and other scrapped items in the scrap yard. One item was a torn notebook of deficiencies recorded during review of your batch manufacturing records. For example, page 22 included a comment on batch **(b)(4)** "not mentioned any deviations of lower yield." Our review of the batch record **(b)(4)** found that the yield reported was **(b)(4)**% (range: **(b)(4)**%), but the batch record did not indicate a deviation. In your response of December 26, 2014, you stated that that these were personal notebooks intended only for meeting and other discussion notes. Your response did not explain why your production personnel used unofficial paper for documenting CGMP relevant data. Your response also did not explain whether the lower-yield event was investigated. Your batch records	

			should include complete information related to the manufacture of each batch, including notation of any deviation, its evaluation, and investigation. Your response is also inadequate in that the investigation you performed in response to FDA's inspection was primarily limited to the discarded CGMP records cited in the Form FDA-483. Your investigation did not include a comprehensive review of all records in the waste area or a thorough review of your firm's practice of destroying CGMP records. In response to this letter, indicate the steps you have taken to ensure all CGMP activities are recorded at the time they occur and that the use of unofficial documentation (e.g., notebooks) has been discontinued. Describe how you will prevent this practice in the future. Also describe improvements to your systems for managing and retaining all CGMP records. Provide your revised record retention policy for all CGMP records. Demonstrate that you have implemented controls over record disposition that include, at a minimum, identification of appropriate documents, retention timelines, clear documentation of what record is destroyed, and names and signatures of those who witnessed the destruction. c. On their December 1, 2014 walk-through of the Zyfine **(b)(4)** plant, our investigators reviewed AHU/HVAC filter cleaning records. Duplicate records were in the engineering office. One of your firm's representatives stated that the records were rewritten for clarity. Our review of the original and rewritten records found discrepancies in cleaning dates and cleaning personnel. Your December 26, 2014 response stated that poor documentation practices resulted from not operating under a corporate quality assurance structure until 2013. In your response to this letter, describe your investigation into discrepancies in the filter cleaning records. Outline the extent of the lack of corporate quality assurance you described in your December 26, 2014 response and systems affected by this critical problem. Provide a summary of your findings, including instances of records that were duplicated or rewritten and any discrepancies found, and describe your CAPA.	

23 Dec 2015	*Cadila Healthcare*	India	**B. Cadila Healthcare Limited India (Zyfine) (FEI 3006595385)** **COMMENT:** These examples (B1 and B2) of our findings at your Zyfine facility raise serious concerns about the effectiveness of your manufacturing controls, the integrity of your computerized records, and the accuracy of your CGMP records. In addition to the specific items requested above, in your response to this letter, provide the following: • A comprehensive investigation and evaluation into the failures underlying these violations. Describe your methodology, including the role of an independent third party if you choose to engage one. Include detailed conclusions about the extent of your data integrity deficiencies and their root causes, which may involve lack of record control, non-contemporaneous recording, deletion of data, and other problems with the integrity of data. • A risk assessment of how the observed deficiencies may affect the reliability and completeness of quality information available for your drug products. Also determine the consequences of your deficient documentation practices on the quality of drug products released for distribution. • A comprehensive management strategy to address these serious breaches, including a detailed global CAPA. The CAPA should include: • A description of the corrective actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, monitoring complaints, reporting any issues affecting drug applications, and other steps to assure the quality of your products manufactured under the violative conditions discussed above • A description of the preventive actions you have taken or will take, such as upgrading systems, revising procedures, implementing new controls, training or re-training personnel, and other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.	NO
31 Dec 2015	*Zhejiang Hisun Pharmaceutical Co., Ltd.*	China	**1. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.**	YES 9/9/15

			During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data and paper records. Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards. Our investigators found that your firm routinely re-tested samples without justification and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts, on multiple pieces of testing equipment, and for multiple drugs. You are responsible for determining the causes of these deviations, for preventing recurrence, and for preventing other deviations from CGMP. a. During the inspection, we reviewed the electronic log for high performance liquid chromatography (HPLC) system #36 and determined that the audit trail was disabled on February 6, 2014. One of your analysts executed 80 HPLC injections for assay and impurity tests of validation stability batches **(b)(4)** of **(b)(4)** API. Because the audit trail was disabled, neither your quality unit nor your laboratory staff could demonstrate that records for these batches included complete and unaltered data. All supporting raw data was discarded, including sample solution dilutions and balance weight printouts. Sample analyses were not recorded in the instrument use logbook. Test results were deleted from the hard drive and all supporting chromatograms were discarded. Audit trail functions were re-enabled on February 8, 2014, and the same analyses were repeated. You submitted the February 8th test results to the FDA in March 2014 in support of Drug Master File (DMF) **(b)(4)** During the inspection, we asked the analyst who generated the data submitted to the FDA whether audit trails could be disabled. The analyst stated that another employee, who was no longer with the company, had disabled the audit trails. Your firm could not explain why the audit trail was disabled or why the original data was deleted, nor could you demonstrate whether the original results were within specification.	

			In your response, you assumed that the original raw data was deleted because a system suitability failure invalidated the data. You acknowledged that the data should not have been invalidated without an investigation of the laboratory event. However, your response is inadequate. There is no evidence to support invalidation of the original data on the grounds of a system suitability failure because your firm deleted all of the original records associated with these analyses. b. While reviewing the electronic log for HPLC system #28, we determined that two of your analysts deleted portions of HPLC sample sequence 20140221 during assay, impurities, and identity testing for **(b)(4)** API batches **(b)(4)**, and **(b)(4)**. During the inspection, the investigator reviewed the data package that your firm used for batch release decisions for this drug. This data package included results from 44 HPLC injections. However, the electronic audit trail from the instrument used to generate these results showed that there were a total of 61 injections. Raw data for 17 of the 61 injections was deleted from the reported sequence as if the injections had never been performed. The investigator later discovered the missing data in a backup folder. You stated in your response that these specific API batches "were sold to [the] Chinese market" and that you planned to retest batches **(b)(4)** to determine whether they are within specification. You also stated in your response that the missing portions of the sample sequence were actually injections conducted for training, so product quality was not affected by the deletions. This response is inadequate, because, regardless of the reason for conducting the injections, your laboratory records must retain all original raw data. c. While reviewing the audit trail on HPLC system #28, we determined that one of your analysts performed trial HPLC injections during assay and impurities testing for batches of **(b)(4)** API (**(b)(4)** and **(b)(4)**). These trial injections were performed on May 4-6, 2014. The data for the sample set was deleted from the system. Testing was not recorded in the instrument use	

			logbook. All supporting electronic raw data was discarded. Testing results for these batches were then recorded on May 7, 2014, when the analyses were repeated using HPLC system #32. During our inspection, one of your analysts provided the original analyses worksheets to review. According to this analyst, tests were repeated because of poor column efficiency. The analyst neither initiated an investigation of the laboratory event nor documented the original analyses in the instrument use logbook. The analyst did not respond when we asked why the initial chromatograms were deleted. However, in your written response, you claimed that this analyst later recalled deleting the data (chromatogram) because column inefficiency may have invalidated the data. Your quality unit must review all pertinent analytical data when making batch release decisions. When analysts delete nonconforming test results, the quality unit is presented with incomplete and inaccurate information about the quality of the products. Your response does not demonstrate how your laboratory procedures prevent the deletion of data or how the quality unit ensures that the records relied upon for batch release and other quality review decisions are complete and accurate. Our concerns about deletion of data are heightened by the significant number of customer complaints for subpotency and out-of-specification (OOS) impurity levels from 2012-2014. We observed data deletion in your laboratory related to assay and impurity levels during this time period. During the inspection, we asked to review your lab's raw analytical data of the lots associated with four of the 61 complaints. However, you were unable to provide the raw data because it had been deleted. Without raw test data for the lots associated with these complaints, your firm could not adequately investigate the complaints, nor could you expand your investigation to determine whether other lots were affected by the same problems or take corrective actions, such as recalling drugs if appropriate. We acknowledge your commitment to hire a third-party consultant, set up user access restrictions, and upgrade computerized systems with audit	

			trails. However, simply activating audit trail functions and instituting password controls are insufficient to correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence. Your management is responsible for the assuring that the scope and extent of the third party audit is adequate, including a full evaluation of sophisticated electronic systems and their potential for manipulation. Your management is also responsible for fully documenting and preserving records. For more information about handling OOS results and documentation of your investigations, please refer to *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf and *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Records and Reports* at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm In your response to this letter, provide the following: A comprehensive investigation and evaluation. Describe your methodology. Results should include conclusions about the extent of data integrity deficiencies and their root causes, which may involve record control, contemporaneous recording, deletion of data, and other data integrity deficiencies. A risk assessment of how the observed deficiencies may affect the reliability and completeness of quality information available for your drugs. Also determine the consequences of your deficient documentation practices on the quality of drugs released for distribution. A management strategy that includes a detailed global corrective action and preventive action plan. Describe the actions you will take, such as contacting your customers, recalling drugs, conducting additional testing and/or adding lots to your stability programs, or other steps to assure the quality of your drugs manufactured under the deficient conditions discussed above.	

			Describe the actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP deviations, including breaches of data integrity.	
31 Dec 2015	*Zhejiang Hisun Pharmaceutical Co., Ltd.*	China	**2. Failure to conduct appropriate microbiological testing on API batches where microbial quality is specified**. On March 2, 2015, we observed that all 14 culture media plates in incubator #6 were dried out and cracked, which compromised microbial growth promotion and accurate enumeration. These plates were used to test multiple API batches of **(b)(4)** and **(b)(4)** and **(b)(4)**). Your investigation concluded that deformed glass plates caused the media to crack. In your response, you claimed that the issue was isolated to the 14 culture media plates and that you retested these **(b)(4)** batches. Your response is inadequate because your investigation did not evaluate the **(b)(4)** other associated batches tested with culture media plates from the same lot containing deformed glass plates. In addition, we disagree with your claim that these dried culture media plates were isolated to the 14 plates we observed on March 2, 2015. On March 5, 2015, we observed two additional culture media plates in incubator SPX-150, Series No. 061103-811-0003, which also showed signs of drying out. From 2012 to 2014, several of your customers complained that microbial results were OOS when they tested your API upon receipt. In your response, you concluded that the percentage of customer complaints reporting OOS microbial test results was insignificant. You attributed the customers' OOS microbial results to test methods that differ from your own.	

			Your response lacks your findings and corrective actions from your recent investigation of dried out and cracked culture media plates. For example, you did not retest the batches that received OOS microbial complaints, even after we pointed out this deficiency. You lack scientific justification to conclude that your customers' OOS findings are inaccurate or insignificant. In your response to this letter, provide the following: An accelerated timeline for completing retroactive microbial testing of all potentially-compromised batches via an independent laboratory, and a commitment to respond with all results promptly. Your review of all microbial test methods to ensure they are suitable for their intended use. A detailed update on whether your firm has implemented any further risk mitigations, such as purchasing prepared culture plates from qualified outside vendors. Your improved deviation and corrective action and preventive action management procedure. Documentation of all changes implemented as a result of your review and remediation of these issues.	
31 Dec 2015	*Zhejiang Hisun Pharmaceutical Co., Ltd.*	China	**COMMENT:** We note that some records we requested during the inspection were not provided in a timely manner. During the inspection, an analyst removed a USB thumb drive from a computer controlling an HPLC. When asked to provide the drive, the analyst instead exited the room with the thumb drive. After approximately 15 minutes, management provided our investigator with what they asserted was the USB thumb drive in question. It is impossible to know whether management provided the same USB thumb drive that the analyst had removed. When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be adulterated under section 501(j) of the FD&C	

			Act. We recommend that you review FDA's guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf	