UNGER CONSULTING INC.

Warning Letters 2016

Data Governance and Data Integrity

In 2015 we published the collection of FDA GMP warning letters that included deficiencies in data governance and data integrity. Here we provide the same information for 2016 drug GMP warning letters. These should serve as a resource for GMP audit staff and QA staff as they evaluate their own firms and contract sites for gaps in these areas. In this introduction, we provide tables and graphs identifying the dates of the warning letters, firms to which they were issued and the country where the facility is located. We also provide a table that shows the trends over time for location of countries where facilities receiving these warning letters were located, beginning in 2008. And finally, we provide a tabulation of the regulations most frequently cited for these deficiencies in 2015 and 2016.

Table 1 lists the warning letters that include data integrity deficiencies, the date of issuance and the country where the facility is located. Note that the first two warning letters were from inspections in 2015 but published in 2016 and were not counted in last years' tally, so I included them here. I've color coded the country column and have included all European countries in a single group.

TABLE 1: Warning Letters with Data Integrity Deficiencies

DATE	COMPANY	Country
12/15/2015	Chan Yat Hing Medicine Factory	China
12/30/2015	Irvine Stem Cell Treatment Center	US
1/29/2016	Ipca Laboratories Limited	India
3/3/2016	Emcure Pharmaceuticals	India
4/1/2016	Sri Krishna Pharmaceuticals Ltd. Unit II	India
4/7/2016	Apotheca Supply Inc	US
4/12/2016	Florida Institute of Reproductive Sciences	USA
4/14/2016	Polydrug Laboatoreis Pvt Ltd	India
5/12/2016	Tai Heng Industry Co Ltd.	China
5/16/2016	BBT Biotech GMBH	Germany
5/19/2016	Megafine Phrma LImited	India
6/16/2016	Shanghai Desno Chemical Pharmaceutical Co.	China
6/21/2016	Chongquing Lummy Pharmacuetical Co	China
6/22/2016	Guuangzhou Haishi Biological Technology Co	China
7/12/2016	GenPak Solutions LLC	USA
7/19/2016	Ziamen Origin Biotech Co Ltd	China
8/2/2016	Adamson Analytical Laboratories Inc.	USA
8/4/2016	Zhejiang Medicine Co Ltd Xinchang Pharmaceutical Factory	China
8/5/2016	Noven Pharmaceuticals	USA
8/10/2016	Hushou Aupower Sanitary Commodity Co Ltd.	China
8/11/2016	Zhejiang Hisoar Pharmaceutical Co	China

8/12/2016	Unimark Remedies Ltd	India
8/15/2016	Frontida	USA
8/25/2016	Pan Drugs Limited	India
8/25/2016	Lima & Pergher Industria e Comercio S.A.	Brazil
9/6/2016	Hebei Yuxing Bio-Engineering Co. Ltd.	China
9/12/2016	Mappel Industria de Embalagens, SA	Brazil
9/15/2016	Nippon Fine Chemical Co.	Japan
9/26/2016	Delarange Cosmetics and Healthcare BV	Netherlands
9/29/2016	Laboratoire Sintyl S.A.	Switzerland
9/29/2016	Yangzhou Hengyuan Daily Chemical Plastic Co Ltd	China
10/13/2016	Teva Pharmacuetial Works Private Limited Company	Hungary
10/18/2016	Interpharm Praha A.S.	Czech Republic
10/19/2016	Beijing Taiyang Pharmaceutical Industry Co Ltd	China
11/8/2016	Sekisui Medical Co Ltd	Japan
11/8/2016	Srikem Laboratories	India
11/10/2016	Dongying Taindong Pharmacutical Co Ltd	China
12/8/2016	Baoying Couonty Fukang Medical Applicance Co. Ltd	China
12/8/2016	Antibioticos Do Brasil Ltda	Brazil
12/15/2016	Natura Bisse International S.A.	Spain
12/23/2016	Wockhardt Limited	India

Table 2 identifies the countries where the facilities are located for both this year's tally and for last year. China was first on the list this year with a significant increase in these type of deficiencies over 2015. India is close behind though with fewer of these type of warning letters than China this year. Note that in CY2016 seven firms in the US received warning letters with data integrity deficiencies. Brazil and Japan are new to the list this year with 3 and 2 warning letters respectively. Figure 1 shows the same information as a graphic.

Table 2: Number of Data Integrity Associated Warning Letters by Country

Country	Number of Warning Letters with Data Integrity	
	CY2015	CY2016
China	2	14
India	10	9
US	0	7
Europe	2	6
Brazil	0	3
Japan	0	2
Thailand	1	0

TOTAL	15	41

Figure 1: Data Integrity Warning Letters by Country

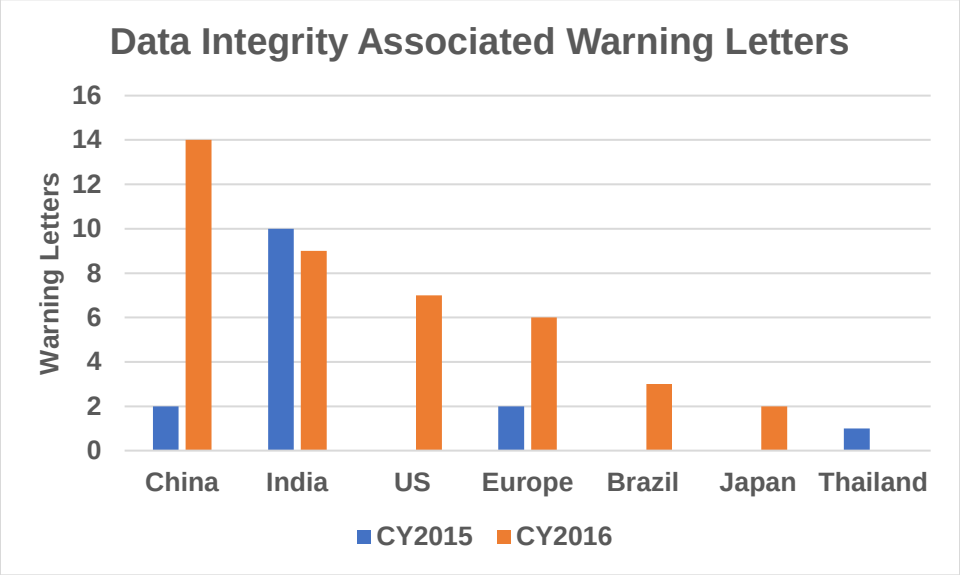

Figure 2 captures data from 2008 through 2016 on a country by country basis. Some countries are consistently present in multiple years including the US, China and India and the 'Europe' category. A few countries are present only in one or two years. Note that the US has warning letters with data integrity deficiencies in *all* years except 2013,2014 and 2015 and is in fact the third most frequent country for 2016 warning letters of this type..

Figure 2

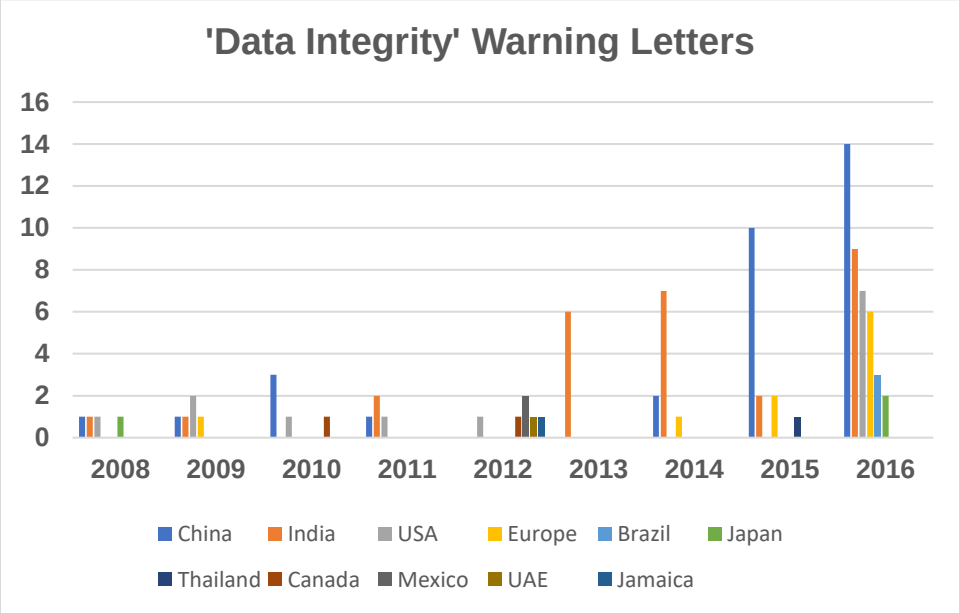

Table 3 shows the regulations cited in the warning letter deficiencies. Many of the deficiencies identified in the collection for CY2016 do not cite a governing regulation. Many are 'conclusions' or 'Data Integrity Remediation' instructions from the FDA to which the firm must respond. Many of the letters are issued to API manufacturers and do not cite 21 CFR 211 which applies to finished product. In addition to the regulations cited below, the following regulations were each cited once: 211.100(b), 1271.50(a), 211.165(e), 211.180(e), 211.137(a), 211.180(a), 211.101, 211.186(a) and 211.42(c). **Table 4** shows the same data for the years 2008-2014. In addition to the regulations cited in the table are 211.25, 211.166, 211.182, and 211.192. As in the past fifteen-plus years, FDA has focused on enforcement of the predicate rules. The notable difference between 2016 and 2008 – 2014 is the appearance of 211.22 and 211.165. For both groups, the categories of "Laboratory", whether controls, records or general requirements is predominant.

Table 3: Most Frequent Regulation Citations in CY2016

CFR Reference	Number of Times Cited	Title of CFR Section
211.68	7	Automatic, Mechanical, and Electronic Equipment
211.22	5	Responsibilities of the Quality Control Unit
211. 194	3	Laboratory Records
211.160	3	General Requirements, Laboratory Controls
211.165	2	Laboratory Controls
211.188	2	Batch Production and Control Records

Table 4: Most Frequent Regulation Citations 2008-2014

CFR Reference	Number of Times Cited	Title of CFR Section
211.68	13	Automatic, Mechanical, and Electronic Equipment
211.194	6	Laboratory Records
211.160	2	General Requirements, Laboratory Controls
211.180	2	General Requirements for Records and Reports
211.186	2	Master Production and Control Records
211.188	2	Batch Production and Control Records

Conclusion:

In 2017 I look for much of the same in terms of warning letter deficiencies in the area of data integrity. I would, however, expect to see more focus on electronic records issues in batch records and in the manufacturing area as FDA expands their focus out from the laboratory. Compliance in this area continues to bedevil the industry, both domestic and foreign manufacturing sites. Perhaps one potential remedy is to have firms' internal GMP audits and assessments focus in depth on this area. Remediation here often takes time and can be expensive if new instrumentation or software is required. But, better to identify problems if they exist than wait to have FDA point them out. Remediation of official health authority actions are necessarily more expensive than finding and correcting issues internally.

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Data Governance and Data Integrity Warning Letters, 2016

Date	Country	Company	Text of Compliance
12/15/2015	China	Chan Yat Hing Medicine Factory	**6. You failed to calibrate and maintain written records for the scale used to weigh components, including active ingredients, prior to their addition into the manufacturing process (21 CFR 211.68(a)).** Your quality unit released multiple batches of drug products for distribution, despite these and other violations.
12/30/2015	US	Irvine Stem Cell Treatment Center	**5. Failure to ensure that batch production and control records are prepared for each batch of drug product produced [21 CFR 211.188].** Specifically, you do not document each significant step in your process, including the major equipment and key personnel used to manufacture your SVF product.
1/29/2016	India	Ipca Laboratories Limited	A. Ratlam facility (FEI: 3002807297) **1. Failure to have computerized systems with sufficient controls to prevent unauthorized access or changes to data.** During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data. 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. During the inspection, our investigators examined the computerized instrumentation and systems you used to conduct chromatographic analyses of your drugs and found that laboratory analysts had PC administrator access that they utilized to manipulate raw data and test results. We found that controls on your computerized chromatographic instrumentation were not adequate to prevent analysts from manipulating processing parameters in order to obtain passing results. We also found that your computerized systems lacked controls to prevent the back-dating of test data. For example, we reviewed the (b)(4) API 12-month (b)(4) Commercial Stability assay test for residual solvent by gas chromatography (GC). For batch #(b)(4) US-DMF ((b)(4)), you reported an (b)(4)% result for (b)(4) residual solvent (specification (b)(4)-(b)(4)%) obtained on July 18, 2013. We documented that the original peak had been integrated inconsistently. Standards and samples had been processed using different integration parameters with no documented reason; there were no controls in the software to prevent analysts from manipulating

			integration settings in order to obtain passing results that you relied on to evaluate the quality of this product. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, an out-of-specification (OOS) value of (b)(4)% was obtained. In the (b)(4) stability interval assay test of the same API, batch #(b)(4) US-DMF ((b)(4)), you reported an (b)(4)% result for (b)(4) residual solvent (specification: (b)(4)-(b)(4)%) obtained on June 12, 2013. We again found that the original sample peaks had been re- reintegrated inconsistently. There were no controls in the software to prevent the inappropriate manipulation of integration parameters. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, the result OOS value of (b)(4)%. For the same test, we found that on and after June 18, 2013, the date and time of the chromatographic injections for the (b)(4) stability test appear to have been set back to June 12, 2013. The data was reprocessed to obtain a passing result, upon which you relied to evaluate the quality of this drug. In addition to these examples of computerized systems that permitted inappropriate manipulation of integration parameters and backdating, our investigators also found several instances of computerized data systems that failed to prevent the deletion of original injections. For example, our investigators reviewed the GC audit trail for (b)(4) (finished API batch #(b)(4)) and found that the original sample injection for related substance was on June 4, 2013 at (b)(4). This injection was aborted with no justification and the computerized system that your laboratory used to capture raw data did not retain the original results. The sample was re-injected at (b)(4)., which automatically deleted the original sample result. Passing results from the re-injection were reported for individual and total impurities. You used these incomplete results to evaluate the quality of this drug. B. The High Performance Liquid Chromatography (HPLC) audit trail for (b)(4) (finished API batch #(b)(4)) shows that the first sample injection for aliquot #2 assay test was on May 28, 2013 at (b)(4). This injection result was deleted without justification. The sample was re-injected at (b)(4). A passing assay result was reported from the re-injection. As with the GC system discussed above, the electronic system your laboratory used to capture HPLC results lacked sufficient controls to prevent the deletion of data without justification, and failed to retain the original data. You relied on these incomplete results to evaluate the quality of this drug. These practices appear to be commonplace in your analytical laboratory. During the inspection, our investigators spoke with an analyst who reported that "…if we find a failure, we set back the date/time setting and re-integrate to achieve passing results…" The analyst explained that deleting, overwriting, changing integration parameters, and altering PC date and time settings were done for raw materials, in-process testing, and finished API drugs. In your response you stated that the stand-alone chromatographic instruments in the Quality Control and Stability laboratories are no longer under full control of individual analysts and

			have been connected to a network-based laboratory system. You also acknowledged that you did not identify all instances of data manipulation that may have led to inaccurate conclusions regarding product quality. However, your response still lacks a comprehensive assessment and retrospective review of data generated from all of your computerized laboratory systems. This includes but is not limited to a risk assessment that evaluates all potentially-affected test data.
3/3/2016	India	Emcure Pharmaceuticals Ltd	**3. 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)).** During our inspection, we observed multiple examples of incomplete, inaccurate, or falsified laboratory records. a. EM records for active air monitoring of the aseptic filling area reported samples as being collected when they were not actually collected, and some records documented purported EM results of zero colony forming units (CFU) even when the samples for which those results were reported were not actually collected. Contemporaneous video recordings that FDA reviewed during the inspection showed that such EM samples had not been collected, even though your laboratory records reported results for those samples. Our investigators observed your firm's practice of falsifying EM results for samples that were not collected for multiple drugs, including **(b)(4)** injection USP lot **(b)(4)** and **(b)(4)** injection lot **(b)(4)**. Although your laboratory records for these products and lots indicated that you collected active air samples, the video we reviewed during the inspection demonstrated that operators did not actually collect the samples. During the inspection, your microbiologist confirmed that these EM samples were never collected. Additionally, two microbiologists informed the investigator that media plates were labeled and submitted for incubation as though they had been exposed to the environment. However, these media plates were never actually exposed to the environment. Your microbiologist indicated that this practice was routine and due to "work pressure." Because the EM results for samples were falsely reported as having been collected and/or as having produced no CFU growth, you lack assurance that the injectable drugs your firm produced in this area were sterile at the end of the aseptic filling process. b. Our review of EM records from January 2014 through September 2014 found that no samples had exceeded the action levels for any of the **(b)(4)** filling lines in your **(b)(4)** plant, or for the filling line in Plant **(b)(4)**. However, we observed 12 microbiological plates in the incubator showing EM results that required further action during our inspection of your laboratory.

			These EM records provide critical data on environmental trends and whether environmental control is maintained during aseptic filling of a batch. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs. In your response, you stated "there have been serious gaps in the management, oversight and execution of the environmental monitoring program, especially with respect to the suspected data integrity and falsification of data concerns." Your response also indicated that you revised procedures, provided training, and reviewed documents from March 2013 to January 2015. Your investigation confirmed that EM samples were not collected and "the data was fraudulent." You acknowledged these problems in your response and took some corrective actions. However, your response is inadequate because you have not demonstrated how you can ensure that EM records generated before the inspection were reliable and accurate, or how the falsification of some of your reported EM data may have affected the quality of your products. We acknowledge your **(b)(4)** after the inspection, your management changes, and your engagement with consultants. However, your investigation was not extended to all systems and areas that may have been affected by your questionable practices. You have not provided data sufficient to demonstrate that all products released for distribution were manufactured with the appropriate environmental controls in place during aseptic filling operations. Furthermore, data falsification and manipulation, and your reliance on incomplete records to release product to the market, are repeat violations. A February 2014 inspection of solid **(b)(4)** dosage operations at this same facility also reported data manipulation and falsification of test results generated by your firm, along with other deficient laboratory practices that also resulted in products being recalled from the U.S. market. In your 2014 response, you made a similar commitment to hire a third party auditor to conduct a comprehensive audit of all laboratory electronic and hard copy data for tests conducted for all release and stability finished product. Our 2015 inspection found continuing practices of data falsification and manipulation at your facility, indicating that previous corrections were ineffective. c. Our investigators observed poor documentation practices during production and in-process testing. *i.* Media fill batch **(b)(4)** documented a "check by" operation performed by an operator who was not present at the facility. This operator signed "checked by" for 63 out of **(b)(4)** individual **(b)(4)**. In addition, during this media fill, a Quality Assurance (QA) individual signed "checked by" for observing the intervention "**(b)(4)** of conveyor belt" from **(b)(4)** to **(b)(4)** on December 2, 2014, but

			the QA individual was not present in the filling room when this intervention was performed, and did not view it. Your response admitted that the individual signing the QA "checked by" column was not present during that portion of the media fill **(b)(4)** to **(b)(4)** on December 2, 2014. *ii.* Disinfection of the filling machine was not completed before filling of **(b)(4)** injection USP batch **(b)(4)** (aseptically filled, **(b)(4)**, and distributed to the U.S. market). Records were made for cleaning on November 13, 2014, from **(b)(4)** to **(b)(4)**, but review of videos show that cleaning did not match records. Your response confirms that the cleaning and disinfection did not occur on November 13, 2014. *iii.* On January 29, 2015, an operator performed in-process weight checks for **(b)(4)** during the filling operation performed at 13:30. This activity was not documented until 14:15. In addition, another weight check operation performed at **(b)(4)** had not been documented on the record when reviewed at **(b)(4)** by the inspector. Your response indicated that activities that occurred on January 29, 2015, are deviations. *iv.* Cleaning of the **(b)(4)** and parts of the filling machine was not completed before filling **(b)(4)** injection USP batch **(b)(4)** (aseptically filled, **(b)(4)**, and distributed to the U.S. market). Records were made for cleaning on November 26, 2014, from 08:57 to 09:26, but videos show that cleaning did not match records. Your response indicates that the cleaning and sanitization of the conveyor **(b)(4)** was missed on one side. Your investigation into this issue is inadequate because it did not consider other in-process tests, or whether the operator(s) have been involved in the same poor documentation practices for others batches. Your response lacks an assessment of your documentation practices to determine the extent of the problem in your facility.
3/3/2016	India	Emcure Pharmaceuticals Ltd	Within 15 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations. In addition to the specific requests noted above, supporting documentation should include your third party assessment of the following. 1. A comprehensive evaluation of the extent of the inaccuracy of your recorded and reported data.

			Include a detailed action plan to fully investigate the extent of your deficient documentation and data management practices. 2. A risk assessment of the potential effects of observed failures on the quality of your drug products, including the effects of deficient documentation and data management practices, aseptic processing breaches, and inadequate environmental monitoring program. Determine the effects of your failures on the quality of drug products released for distribution and the data supporting all associated submissions. 3. A management strategy for your firm that includes the details of your 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. Also indicate measures you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other actions to prevent the recurrence of CGMP violations, including breaches of data integrity.
4/1/2016	India	Sri Krishna Pharmaceuticals Ltd - Unit II	**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)).** Your laboratory records did not contain all raw data generated during each test for finished drug products manufactured at your firm. Your quality unit relied on incomplete records to make batch release decisions in support of regulatory submissions to the Agency. During the inspection, your management acknowledged that employees in your QC laboratories conduct trial HPLC injections prior to the injections submitted as the reported test results. These trial injection data files were stored on separate drives from the reported test result data. In some cases original data files were deleted. The results from these trial injections and other original data were not reported. Our investigator found the following examples: a. A QC analyst injected eleven identically or similarly named samples for impurity and assay analysis approximately one to fifteen seconds apart from one another, according to the HPLC audit trail for (b)(4) DMF submission batches (b)(4) and (b)(4). A second analyst injected eight similarly named impurity and assay samples approximately twelve to sixteen seconds apart, according to the HPLC audit trail for the analysis of (b)(4) batches(b)(4) and (b)(4). Neither analyst reported all results obtained during testing. The laboratory incident reports concluded the first analyst deleted 28

			original files due to pressure fluctuations and ghost peaks, while the second analyst deleted original trial injections of working standard and sample testing data due to a problem associated with peak shape. However, your laboratory incident reports provide no evidence to support these conclusions. Both analysts also changed the clock prior to reanalyzing the samples. b. A QC analyst injected sample P140818008.lcd for the assay analysis of (b)(4) (batch (b)(4)) prior to the reported sample injections. The “trails” [sic] folder where the original sample injection file was saved had been deleted. Your response acknowledges that an analyst deleted eight injections, including the blank, six standards, and a sample. c. A QC analyst deleted original test method validation data and admitted plans to fabricate sample preparation data. According to the HPLC audit trail, on October 7 and 8, the QC analyst injected two sets of similarly named samples of (b)(4) (#1:P141007001.lcd and #1:P 141007001.lcd) for an impurity analysis method validation study. Your analyst deleted data from the first set of injections and submitted only the second set in the validation documentation. The analyst stated that he planned to back-date the preparation data within the worksheets once all testing was complete. However, aside from balance scale tickets, your firm was unable to provide sample preparation data for either sample. Your response states that you abandoned the method validation study, but you continue to use that method for routine testing. In response to this letter, provide the method validation study that supports your current method for analyzing impurities in (b)(4). d. You did not include metadata with audit trails in your (b)(4) data back-up. In November 2014 the system for HPLC #025 crashed and lost all data collected on the instrument, including audit trail information. We acknowledge that you have implemented (b)(4) and (b)(4) system back-ups. In your response to this letter, provide a copy of the associated procedures and details on how the back-ups are performed. e. Prior to October 2014, your gas chromatography instrument sent injection data to PCs without audit trails. The instrument logbook documented analyses that did not appear in the audit trail after your firm said it turned on the audit trail function. Your response does not explain the missing injection data. In response to this letter, compare the logbook and the audit trail and provide an explanation for the discrepancies identified during the inspection. f. A QC analyst injected sample (b)(4)141119009 for the assay analysis of (b)(4) batch (b)(4), prior to the reported sample injection. The trial injection was stored in the “trails” [sic] folder located on a personal computer. The release chromatogram identified injection (b)(4)141119009 as the sample. The trial and release chromatograms for (b)(4)141119009 do not match, and they identify different

			peaks. Your response concluded trial injection (b)(4)141119009 was a blank. However, the chromatogram for (b)(4)141119009, collected during the inspection, shows (b)(4) peaks. You do not explain or provide evidence for how you concluded that this injection was a blank. Furthermore, your response includes a chromatogram for trial injection (b)(4)141119009 that differs from the chromatogram our investigator collected. It appears to have been reintegrated; the y-axis scale was changed, and only two of the original (b)(4) peaks can be seen. When analysts delete nonconforming test results, the quality unit is presented with incomplete and inaccurate information about the quality of the products. None of your explanations justify your failure to maintain complete records, nor do they support your practice of repeating tests or deleting test results.
4/1/2016	India	Sri Krishna Pharmaceuticals Ltd - Unit II	**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)).** During the inspection, our investigator reviewed data from your high-performance liquid chromatography (HPLC) analysis for release testing, including assay and impurity testing. Your quality control analysts used administrator privileges to change the controls for the time and date settings and manipulate file names to overwrite injections and delete original HPLC test data. Analysts also routinely turned HPLC audit trails on and off. Your response acknowledges these practices. During the inspection the investigator also noted the following examples of uncontrolled access to electronic systems used to generate data: a. None of the (b)(4) HPLC instruments in your QC laboratory required user-specific log-in names and passwords. Analysts routinely logged in as “Admin” without a password. Your response failed to provide a detailed description of the user roles and responsibilities associated with each instrument in your QC laboratory. In your response to this letter, provide procedures that address user roles and associated privileges for your laboratory instruments. b. Laboratory data generated by the Karl Fischer autotitrator was not restricted. The program used to run your autotitrator, Tiamo™ 2.3 Light, is unable to record audit trails and cannot support accounts with unique user names and passwords for individual users. We acknowledge your commitment to upgrade to a compliant software package. However, your response is inadequate because you failed to provide an interim solution prior to its installation. In your response to this

			letter, provide a copy of the performance qualification and training activities associated with the newly purchased software. c. Your analysts created separate folders on personal computers to store data from trial HPLC injections. For example, during the inspection, our investigator found a data folder labeled “trails” [sic]. In response to this letter, provide an assessment of the content of these folders and an evaluation of results that may not have been investigated. We acknowledge your commitment to set up user access restrictions, discontinue the practice of trial injections, and to institute audit trails for computerized systems. Simply activating audit trail functions and instituting user controls are insufficient to correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence. Your response is inadequate because the functions and administrative privileges of the IT Head, QC Head, and other personnel remain unclear. In your response, clarify the specific user roles and associated privileges for each laboratory system, and provide an assessment of the effectiveness of these newly implemented system controls. Also, provide a comprehensive assessment of other updates made to your computerized systems.
4/1/2016	India	Sri Krishna Pharmaceuticals Ltd - Unit II	**3. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to document same at the time of performance (21 CFR 211.100(b)).** Our investigator discovered that your firm was destroying original batch records and backdating revised replacement pages. For example, our investigator found original pages from five **(b)(4)** batch records (batches **(b)(4)** to **(b)(4)**) discarded outside your facility. Your quality control unit approved revised and backdated master batch record pages that your firm created to replace the discarded pages. The original data were subsequently transcribed and backdated to the time of production. Quality and production managers allowed this practice. Your response indicated that your firm would not permit backdating in the future and that you would revise procedures to ensure reissued batch record pages are documented in the incident report register and a change control would be initiated for any minor editorial changes. In response to this letter, provide copies of the revised procedures and an assessment of how widespread the practice of revising and backdating batch records is.

4/1/2016	India	Sri Krishna Pharmaceuticals Ltd - Unit II	**Conclusion** The examples above are serious CGMP violations 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 observed similar issues at your facility in 2007. At that time we found you had improperly integrated HPLC peaks and had not identified and investigated out-of-specification test results. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. However, it is your responsibility to ensure that any third-party audit appropriately evaluates the vulnerability of your sophisticated electronic systems to data manipulation. It is also your responsibility to ensure that follow-up actions fully resolve all of your violations. In response to this letter, provide the following. 1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that you engage a qualified third-party consultant with specific expertise in the areas where potential breaches were identified to evaluate all data integrity lapses. 2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

			3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities that are already underway or completed. 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.
4/7/2016	US	Apotheca Supply Inc	**2. Your firm failed to have stability data to support the extension of expiration dates.** You extended API manufacturers' expiration dates by as much as two years and listed the new expiration dates in your CoAs for APIs repackaged at your facility. You tested APIs to verify that the results complied with the manufacturers' specifications. However, you did not perform stability testing to ensure that APIs met all specifications for the expiration dates you listed on your CoAs. You have no scientific justification for extending the expiration dates. For example, our investigator found unsupported extension of expiration dates for the following APIs:
4/12/2016	US	Florida Institute of Reproductive Sciences	**1. Failure to determine eligibility based on donor screening in accordance with 1271.75 and donor testing in accordance with 1271.80 and 1271.85. A responsible person, as defined in 1271.3(t), must determine and document the eligibility of a cell or tissue donor [21 CFR 1271.50(a)].** Specifically:

			a. There is no documentationon file that a Donor Eligibility determination was made by the responsible person for directed semen donors **(b)(6)** and **(b)(6)**. b. Donors were determined eligible before communicable testing results were received. For example: • A specimen for communicable disease testing was collected from directed semen donor **(b)(6)** on June 1, 2015. The donor, **(b)(6)**, was determined to be eligible on June 1, 2015, but the results were not reported until June 4, 2015. • A specimen for communicable disease testing was collected from oocyte donor **(b)(6)** on January 23, 2015. The donor, **(b)(6)**, was determined to be eligible on January 23, 2015, but the results were not reported until January 26, 2015. • A specimen for communicable disease testing was collected from oocyte donor **(b)(6)** (formerly **(b)(6)**) on March 17, 2015. The donor was determined to be eligible on March 13, 2015, but the results were not reported until March 19, 2015.
4/14/2016	India	Polydrug Laboratories Pvt Ltd	**1. Failure to record and investigate all quality-related customer complaints according to an established procedure.** During the inspection our investigator found a torn sheet of paper titled "Product Quality Complaints" on the floor of your warehouse. We compared it to your firm's official complaint log and discovered that only 2 of the 17 customer complaints on the torn sheet were recorded in your firm's official complaint log. Further, your firm indicated that there may be additional unlogged and/or uninvestigated complaints, but did not provide further explanation. Your firm had not investigated the complaints we found on the torn sheet. These uninvestigated complaints reported API that were either sub-potent or contained filth, including the following problems: • low assay value for **(b)(4)** API • particles and hairs in **(b)(4)** API • an insect and dirt in **(b)(4)** API • safety goggles in **(b)(4)** API • **(b)(4)** scoop in **(b)(4)** API Your response stated that you will initiate a corrective action and preventive action (CAPA) plan to include your quality unit's assessment of your current practices. Your response is inadequate because it is silent on any retrospective investigations conducted for the 17 complaints that our investigator found on the sheet of paper on your warehouse floor. Your

			response also did not specify improvements to your complaint handling procedures and documentation practices or efforts to locate and investigate any other unlogged and/or uninvestigated complaints that your firm acknowledged could exist. Although the 17 complaints in the unofficial log were not from U.S. customers, your firm uses shared equipment, personnel, and materials to manufacture products for multiple markets, including the United States. Your firm's poor complaint handling practices and your inability to prevent and detect product quality defects, such as filth, indicate significant lapses in your firm's quality system. You are responsible for ensuring that prior to release your API meet quality and safety requirements and for assuring that any subsequent quality defects are thoroughly investigated. You are also responsible for taking appropriate corrective actions and preventive actions. In response to this letter, provide the following: • a summary of your investigations of all complaints received since 2012, noting whether each complaint is logged in your official complaint log and including root cause determinations and CAPA • your improved complaint handling procedure and details of any further controls implemented to ensure that all complaints are logged, documented, and promptly investigated
4/14/2016	India	Polydrug Laboratories Pvt Ltd	**2. Failure to review and investigate all production deviations.** Our investigator found a torn page from a batch production record for lot **(b)(4)** of API **(b)(4)** in the trash. He noted discrepancies between the discarded page and the complete batch production record that your firm represented as the official record for that lot. Your firm did not investigate this deviation or the unacceptable practice of discarding a manufacturing record. You did not determine the root cause or assess its effect on drug quality prior to releasing lot **(b)(4)**. Your response states that your quality unit is working on a system to record original data at the time it is generated. However, your response is inadequate because you failed to indicate whether you intend to retrospectively investigate the extent to which your firm's manufacturing records are unreliable, determine root causes, and take necessary corrective actions. Further, you did not note whether your quality unit will conduct a thorough review of all batch production records for accuracy and investigate any discrepancies. In response to this letter, provide the following: • a summary of your retrospective investigation of the duplicate batch production records for lot **(b)(4)**

			• a retrospective review of all batch production records for lots within expiry, including an evaluation of the effect of any discrepancies on API batch quality • your CAPA plan describing actions and controls to ensure accuracy and retention of all records including original batch production records • documentation that your employees are adequately trained to complete batch production records contemporaneously and accurately, to investigate production record discrepancies, and to understand the connection between accurate recordkeeping and product quality
4/14/2016	India	Polydrug Laboratories Pvt Ltd	**3. Failure of computerized systems to have sufficient controls to prevent unauthorized access or changes to data.** Your firm's computer system for entering test results and storing certificates of analysis (CoA), which document whether a drug meets specifications, does not have sufficient controls to prevent unauthorized changes to a CoA after quality unit approval. During the inspection, our investigator reviewed **(b)(4)** CoA stored on computer #16, all of which were approved by the quality unit. A manager demonstrated for our investigator how results on an already finalized CoA could be manipulated after the formal quality unit approval. Also, the quality unit's electronic signatures on these CoA were uncontrolled images of signatures rather than certificate-based electronic signatures. Your response states that your firm plans to implement an enterprise resource planning system. Your response is inadequate because you did not provide sufficient detail about how this system will prevent unauthorized access or data manipulation, nor did you indicate your timeframe for installing and validating the system. In addition, you failed to review and confirm authenticity of CoA data for products you have already released under the deficient conditions described above. In response to this letter, provide the following: • a CAPA plan for controlling access to computer systems for all laboratory and manufacturing records and equipment • your firm's plan to establish, issue, and strictly control access to your manufacturing and laboratory systems • a detailed summary of your steps to train personnel on the proper use of computerized systems

4/14/2016	India	Polydrug Laboratories Pvt Ltd	Conclusion Deviations cited in this letter are not intended to be an all-inclusive list. 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. Your quality system does not securely and reliably retain your manufacturing data and records. We acknowledge your ongoing work with your own subject matter experts to identify root causes of the deficiencies. In addition, we strongly recommend that you engage a third-party consultant with appropriate CGMP expertise to assess your firm's facilities, procedures, processes, systems and data integrity to ensure the identity, strength, quality, and purity of the API you manufacture. In addition to the specific items requested above, include the following in your response: 1. A comprehensive investigation into the extent of the inaccuracies in data, records and reporting. Your investigation should include: - A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. - Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. - An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. 2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. 3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: - A detailed corrective action plan that describes how you intend to ensure the reliability and

			completeness of all of your firm's data. - A comprehensive description of the root causes of your data inaccuracies, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. - Interim measures describing the actions you have taken or will take to ensure the quality of your drugs, such as notifying your customers, conducting additional testing, recalling product, adding lots to your stability programs to assure stability, and enhanced complaint monitoring. - Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
5/16/2016	Germany	BBT Biotech GMBH	**Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.** Our investigator found that your **(b)(4)** system used for **(b)(4)** and **(b)(4)** testing lacked access controls and audit trail capabilities. For example, all employees had administrator privileges and shared one user name, so actions could not be attributed or traced to specific individuals. This exposed your electronic data to manipulation and/or deletion without traceability. Our investigator also noted that your firm copied raw data to a CD **(b)(4)**, and then deleted the data from the **(b)(4)** system to free space on the hard drive. Files copied to the CD were selected manually; the selection process was not supervised. Without audit trail capabilities or supervised file selection, there was no assurance that all raw data files were copied to the CD before they were permanently deleted from the system. We acknowledge your commitment to hire a third-party expert to install audit trails and other controls to ensure that data cannot be deleted from this electronic system. However, your response was inadequate. Simply preventing data deletion is not sufficient. You did not show how these steps will ensure that your firm retains and evaluates all data, including laboratory data, created as part of a CGMP record prior to release of your API. In your response to this letter, investigate your retention and review of CGMP data and provide the results. Focus on your firm's review and retention of laboratory raw data. In addition, provide your interim plan for reviewing and retaining data while your firm is in the process of implementing access controls and audit trail capabilities.

5/16/2016	Germany	BBT Biotech GMBH	**1. Failure to follow a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.** You did not follow your stability program, SOP No. Q-0007. According to your SOP, you must fully test at least **(b)(4)** batch of **(b)(4)** API **(b)(4)** for stability at defined stability intervals. Your firm could not provide any stability data to support the **(b)(4)** expiration date assigned to your **(b)(4)** API. For example, since January 2012, you shipped approximately **(b)(4)** batches of **(b)(4)** API to the United States for which you have no stability data to support your expiration dates. Without stability data for your API, you could not assure that your API met specifications when used by your customers. We acknowledge your commitment to follow your SOP and perform the required stability testing on future batches. However, your response was inadequate because you failed to include any retesting of the API already distributed. In response to this letter, provide data evaluating whether all API batches potentially in United States supply chain within expiry are stable for the assigned **(b)(4)** expiration date.	
5/12/2016	China	Tai Heng Industry Co., Ltd.	**1. Failure to adequately investigate out-of-specification results and implement appropriate corrective actions.** The investigator found that batch samples were routinely retested following failing or atypical results until acceptable results were obtained. Failing or atypical results were not investigated or included in official laboratory control records.	
5/12/2016	China	Tai Heng Industry Co., Ltd.	**2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.** During the inspection, an FDA investigator 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 investigator 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 and on multiple pieces of testing equipment.	

			Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events.
5/12/2016	China	Tai Heng Industry Co., Ltd.	**3. Failure to record activities at the time they are performed, and destruction of raw data.** Your employees did not complete batch production and control records immediately after activities were performed. Your operators used "mock" sheets (copies of the uncontrolled copy of the master production records) to capture critical manufacturing data. Your employees then completed and backdated batch production records days after operations ended. Our investigator noted discrepancies between the "mock" sheets and the complete batch production record that your firm represented as the official record for that lot. Because of your uncontrolled documentation practices, you could not produce evidence that your batch production records were accurate. Batch production records must be generated contemporaneously and include complete and accurate information on the production and control of each batch. The practice of using unbound, uncontrolled loose paper, in conjunction with backdating records, raises additional concerns about the integrity, authenticity, and reliability of all your data, and the quality of your API.
5/12/2016	China	Tai Heng Industry Co., Ltd.	**In conclusion:** In your response to this letter, provide the following. 1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: o A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. o Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. o An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. o A comprehensive retrospective evaluation of the nature of all data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified should evaluate all data integrity lapses.

			2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include *analyses* of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. 3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: o A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. o A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. o Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. o Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. o A status report for any of the above activities that are already underway or completed.
5/19/2016	India	Megafine Pharma Limited	**1. Failure to ensure that, for each batch of intermediate and API, appropriate laboratory tests are conducted to determine conformance to specifications.** One of your analysts acknowledged falsifying test data for **(b)(4)** stability batch **(b)(4)** in August 2012. The analyst substituted a reference standard chromatogram in place of the 12-month stability interval chromatogram. You also submitted this data to FDA in support of drug master file (DMF) **(b)(4)**. In your response, you stated that laboratory management did not discover the discrepancy until the 24-month stability interval. You also stated that the batch quality is unaffected because subsequent test results met specifications at the 24-month and 36-month stability intervals. Your response is inadequate because it does not address the extent of the data falsification that could exist in your laboratory. You have not provided the results of any investigation to determine the accuracy of the test data for other batches of drugs and the corrective actions that should be implemented to ensure the quality of the drugs intended for U.S. distribution.

			In response to this letter, conduct a complete review of all data submitted to the agency in support of DMF **(b)(4)** and provide a detailed assessment of any discrepancies found. Also provide a review of all test results for any **(b)(4)** batch released for U.S. distribution within expiry.
5/19/2016	India	Megafine Pharma Limited	**2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent manipulation and omission of data.** Multiple analysts, testing multiple drugs, deleted unknown peaks without justification. These manipulations made the drugs appear to meet their specifications. Of concern, one of these unknown peaks was for a residual solvent known to be a genotoxic impurity. In response to this letter, provide the residual solvent results performed by an independent laboratory for all lots of drugs distributed to the United States.
5/19/2016	India	Megafine Pharma Limited	**Data Integrity Remediation** Your quality system does not adequately ensure the adequacy and integrity of data to support the safety, effectiveness, and quality of drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following: 1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: ○ A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. ○ Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. ○ An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. ○ A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential lapses were identified should evaluate all data integrity lapses. 2. A current risk assessment of the potential effect of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations.

			3. A management strategy that includes the details of your global corrective action and preventive action plan. Your strategy should include: • The detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to the FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities that are already underway or completed.
6/16/2016	China	Shanghai Desano Chemical Pharmaceutical Co	**1. Failure to have laboratory control records that include complete data derived from all tests conducted to ensure compliance with established specifications and standards.** Your laboratory personnel conducted "unofficial" testing without appropriate documentation, justification, and investigation. The original, unofficial analyses were stored in a separate "Test" folder and were not part of the official quality control records. Our inspection found that your firm performed circa 8,400 of these unofficial chromatographic analyses between 2012 and 2014. According to your SOP-B-QC-022-01, *Instrument Use Standard Operating Procedure*, analysis of samples must be documented. The volume of data in these auxiliary "Test Folders" suggests that performing unofficial analyses is a common practice at your facility. Your quality unit must review all pertinent analytical data when making batch release decisions in order to determine batch quality. During the inspection, a member of your staff told our investigator that you were now in the process of reviewing these unofficial analyses. In your post-inspection response, you indicated that some of the analyses were related to out-of-specification (OOS) investigations, and you would review all of the approximately 8,400 injections by

			December, 2015. You also committed to continue reviewing all analytical data generated by your laboratory and to retrain employees. Your response is inadequate because it lacks a comprehensive assessment of your laboratory practices and management oversight. Your response did not provide the extent of the unofficial analyses throughout your laboratory and the products affected.
6/16/2016	China	Shanghai Desano Chemical Pharmaceutical Co	**2. Failure to ensure all production deviations are reported and evaluated, and that critical deviations are investigated and the conclusions are recorded.** Your firm failed to investigate and document a number of production deviations. During the inspection, our investigator found many electronic logs of production deviations in a folder titled "GMP Anomalies." Our investigator randomly selected folder 01/2014 from your electronic log, compared it to your firm's official deviation logbook for 2014, and found that the deviations in the "GMP Anomalies" folder were not investigated or reported in the official deviation logbook. Production deviations included, but were not limited to: • out-of-limit temperature readings for critical process parameters • incomplete batch records • batch records pre-filled before manufacturing • failure to record temperature, humidity, and pressure • failure to add portions of raw materials during manufacturing In your response, you attribute the root cause of these failures to deficient procedures and operators' errors. You stated that you will conduct a retrospective review for all deviations made in the **(b)(4)** products "Production Coordination Log" from January 2014 through April 2015, to determine whether any CGMP deviations may have compromised product quality. Your response is inadequate as your protocol did not include a thorough review of complaints to determine if undocumented deviations could be linked to product quality defects
6/16/2016	China	Shanghai Desano Chemical Pharmaceutical Co	**Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. In response to this letter, provide the following**. 1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

			• A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of all data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified should evaluate all data integrity lapses. 2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. 3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities that are already underway or completed.
6/21/2016	China	Chongqing Lummy	**1. Failure to prevent unauthorized access or changes to data and failure to provide adequate controls to prevent manipulation and omission of data.**

		Pharmaceutical Co	During the inspection, FDA's investigator discovered a lack of basic laboratory controls to prevent changes to and deletions from your firm's electronically-stored data. Your firm relied on incomplete and falsified records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards. Our investigator found that your firm failed to prevent data manipulation on multiple computerized analytical systems. Your firm re-tested samples without justification and deleted raw analytical data from computerized systems. You are responsible for determining the causes of these deviations, for preventing their recurrence, and for preventing other deviations from CGMP. a. Our investigator's review of the audit trail for the residual solvent stability testing indicated that an analyst manipulated your computerized gas chromatography (GC) system to falsify residual solvent stability results for multiple batches of **(b)(4)** API distributed to the U.S. For example, on March 4, 2016, your analyst set the GC personal computer (PC) clock back to make it appear as if testing had been done seven months earlier – on August 3, 2015. The analyst then performed five different injections to produce falsified results for long term stability 25C/65% RH 12 month time-point residual solvent testing for finished API lot **(b)(4)**. The analyst deleted the first four backdated results and reported only the results of the fifth and final injection as passing in the quality control data package. Your quality unit relied on this incomplete data package to evaluate the quality of this lot of API and determine whether it was within specification. Our investigator observed that long-term stability results for at least five other lots of **(b)(4)** API were falsified using this technique of setting back the clock on the GC personal computer and then performing multiple injections until favorable results were obtained. Your firm failed to prevent analysts' access to manipulate and delete laboratory data. In addition, your laboratory equipment lacked software controls to assure data integrity. b. Our investigator's review of the audit trails for the high performance liquid chromatography (HPLC) system indicated that, just prior to the completion of certain stability analyses for **(b)(4)** API, analysts routinely aborted the ongoing tests to prevent your HPLC system from recording some assay and impurities test data. Your HPLC system, controlled by Chemstation software, was configured to automatically delete the results if a test was aborted prior to completion. Our investigator's review of the system's limited audit trails indicated that when an analyst aborted assay and impurities tests, the partial results from the aborted tests were automatically deleted from your computerized HPLC system's records. For example, our investigator reviewed a data file audit trail that showed that during impurities analysis of an 18-month stability sample of **(b)(4)** crude batch **(b)(4)**, your analyst aborted the injection before the test was complete, set the HPLC PC clock back, and then repeated the

			injection. Your analyst only reported the results of the second injection in the quality control data package. This test, for which your computerized system did not retain original data about the quality of your **(b)(4)** crude, had been performed as part of a stability study your firm executed in response to FDA's previous inspection in July, 2013. Our investigator observed the same technique for data manipulation and deletion in multiple other impurities analyses for **(b)(4)**. When our investigator asked your staff about these instances of falsification and manipulation, your quality control manager stated that your firm "forgot" to perform stability testing and therefore created falsified results for each missed time point by manipulating the controlling PC clock. In your response to the FDA-483, you stated that you would upgrade your GC and HPLC software, and revise standard operating procedures (SOPs) for handling analytical data and train your staff on these revised SOPs. You also indicated that you would retrospectively review analytical data, and if data manipulation was identified, conduct a risk assessment to determine whether "re-testing actions are required." Your response is inadequate because you have not demonstrated how the software upgrades, SOP revisions, and training will correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence. Your quality unit must review all pertinent analytical data when making decisions about the quality of your drugs and when evaluating their conformance to established specifications. When your electronic systems permit the falsification and manipulation of data to obscure or delete test results, the quality unit is presented with incomplete and inaccurate information about the quality of your drugs. Your response does not demonstrate how your proposed software upgrades, revised procedures, or training will prevent the deletion of data or how your quality unit ensures that the records relied upon for batch release and other quality review decisions are complete and accurate
6/21/2016	China	Chongqing Lummy Pharmaceutical Co	**2. Failure to document manufacturing operations at the time they are performed.** During the inspection, our investigator reviewed 20 executed batch manufacturing records and found that most of them contained similar or identical entries that could not be adequately explained. For example, our investigator examined batch records for **(b)(4)** different batches of **(b)(4)** API manufactured between January and February 2015. All **(b)(4)** batch records indicated that certain process steps or measurements had transpired at exactly the same time for each different batch. When our investigator asked your production supervisor to explain why the time stamps were identical on these records, the production supervisor stated that the full manufacturing process takes **(b)(4)** to complete, and that all batch records are kept in the production area until **(b)(4)** lots are completed. The production supervisor stated that the operators most likely did

			not record the actions at the time they were performed but rather completed batch records in groups. In your response to the FDA-483, you indicated that you would not release any new **(b)(4)** API to the U.S. market until "FDA deems our facility acceptable." You also indicated that you had reviewed all manufacturing data and found "some batches have the same falsification" and committed to revising your batch manufacturing record template and SOPs, and retraining your staff. Your response was inadequate. Neither revised templates and procedures nor retraining your staff alone can prevent operators from continuing to falsify batch manufacturing records.
6/21/2016	China	Chongqing Lummy Pharmaceutical Co	Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. In your firm's March 31, 2016, response, you admitted that personnel were not properly trained and that you planned to hire a consultant to perform comprehensive CGMP training. You committed to recall your API in your April 29, 2016, correspondence to the Agency. We have since received confirmation from your **(b)(4)** sales agent that you did initiate a voluntarily recall of **(b)(4)** of **(b)(4)** API from your U.S. customers. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. 1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential lapses were identified should evaluate all data integrity lapses. 2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

			3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.A status report for any of the above activities that are already underway or completed.
6/22/2016	China	Guangzhou Haishi Biological Technology Co	**Our investigators observed specific violations including, but not limited to, the following.** 1. Your firm failed to test finished batches of your drug products for the identity and strength of active ingredients (21 CFR 211.165(a)). 2. Your firm failed to conduct at least one specific identity test on a component when relying on that component supplier's analysis (21 CFR 211.84(d)(2)). 3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).
7/12/2016	US	GenPak Solutions LLC	3. Your firm failed to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated (21 CFR 211.22(a)). Your quality control unit failed to review 42 of the 104 batch production records that we looked at during the inspection for accuracy and completeness before you released drug products. Records lacked critical in-process control inspection results for tracking lot

			information, expiration dates, seal integrity, and broken or missing tablets/capsules. For example, your firm distributed prednisone 2mg tablets lot 15010127 on March 19, 2015, but the batch production record for this lot did not include in-process control inspection results and the batch production record was not signed by quality control unit personnel to indicate quality control unit review before release. In your response to this letter, provide the following: • Your steps to ensure that production records are reviewed and approved prior to lot release. • Your steps to review all previously released lots when you find missing in-process data. Include your range of actions and your selection criteria.
7/19/2016	China	Ziamen Origin Biotech Co Ltd	**2. Failure to transfer all quality or regulatory information received from the API manufacturer to your customers.** You repeatedly falsified and omitted information on the certificates of analysis (CoA) you issued to your customers. For example, your firm fabricated the name of an employee, and you used that name as the false signatory authority on the CoA you sent to your customers. You also omitted the name and address of the original API manufacturer and did not include a copy of the original batch certificate. Finally, you included an "expiration date" on your CoA that exceeded the manufacturer's labeled expiration date, but you had no basis for the extended retest/expiry period. Regulators and customers rely on CoA to provide accurate information regarding drug quality and pedigree. Omitting and falsifying information on CoA compromises supply chain accountability and traceability and may put consumers at risk.
7/19/2016	China	Ziamen Origin Biotech Co Ltd	During the inspection, your firm also made misleading or deceptive statements and delayed the investigator's access to accurate and truthful information. For example: • During the inspection, an employee told the investigator that there were no drugs on site. The investigator observed a room adjacent to the conference room that was being used as a warehouse for relabeled drugs. • The same employee told the investigator that your firm stopped relabeling drugs in January, 2015. However, during the inspection, the investigator reviewed an exported drugs list that showed that your firm distributed drugs after January 2015 and into January 2016. 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
8/2/2016	US	Adamson Analytical Laboratories Inc.	**1. 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)).** Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition systems did not have sufficient controls to prevent deletion or alteration of raw data files. During the inspection, our investigators observed that your laboratory personnel use a shared password to access the HPLC **(b)(4)** computer system and that your GC **(b)(4)** computer system requires no password for access. In addition, multiple instruments had no audit trail function to record information about each analytical test, such as: • type of injection • date and time • identity of analyst • reason for action taken (for example, modifying a record) This is a repeat observation from our February 7, 2013, inspection. In 2013, you committed to augmenting the security of your computer systems within six months. However, based on our 2015 inspection, it appears that you have not made appropriate corrective actions such as installing audit trails and ensuring that analysts have unique user names and passwords for your computerized systems. It is essential that your firm keep track of all changes made to your electronic data. The use of audit trails for computerized analytical instrumentation helps to ensure that all additions, deletions, or modifications of information in your electronic records are authorized. It also allows you to verify the quality and integrity of the electronic data your contract testing laboratory generates for your customers. We acknowledge your commitment to install and configure appropriate electronic controls to ensure that access to your computerized systems and data is restricted to authorized personnel with access rights specified for each individual. However, your response is inadequate as you did not provide an action plan describing the interim security measures in place prior to your installation of electronic controls. Your response also lacked details regarding the type of electronic controls to be installed,

			and you did not describe how you will evaluate the effectiveness of these computerized system changes.
8/2/2016	US	Adamson Analytical Laboratories Inc.	**2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b))** Specifically, your quality control unit failed to ensure completeness and accuracy of your laboratory procedures, analytical data, and test results. For example: • You did not detect that your secondary reference standards for oxymetazoline hydrochloride were not appropriately qualified as required by your firm's standard operating procedure (SOP), **(b)(4)**. • You reviewed and approved laboratory notebooks with missing data such as HPLC chromatograms and assay calculations.
8/4/2016	China	Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory	**1. Failure to have laboratory control records that include complete data derived from all tests conducted to ensure compliance with established specifications and standards.** Your laboratory personnel conducted unofficial testing without appropriate documentation, justification, and investigation. Our inspection found that analysts performed multiple gas chromatography (GC) analyses of **(b)(4)** samples for residual solvents. Analysts performed these unofficial analyses and recorded them in separate "R&D" folders before conducting the officially reported sample analyses. The original, unofficial analyses stored in separate R&D folders were not part of the official quality control records for your API, and your firm did not consider the results of these unofficial analyses to evaluate the quality of your API or make batch release decisions for numerous batches of API. Our investigator reviewed chromatograms found in the R&D folders and noted that some displayed large unknown peaks that were not reported in the official records for the same samples. The presence of such peaks in the chromatograms may indicate the presence of unknown and uncharacterized impurities (including potential contaminants) in your drugs. In your response, you stated that from April to July 2013 you performed "pre-trial" sample analyses for residual solvent testing of **(b)(4)** batches to check system suitability. You also stated you were not testing into compliance and attempted to attribute the unknown peaks found in your "pre-trial"

			sample analyses to operator error. FDA considers the use of an actual sample in test, prep, or equilibration runs as a means of disguising testing into compliance, a violation of CGMP.
8/4/2016	China	Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory	**2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.** Our investigator found that your GC system used to test for residual solvents in **(b)(4)** lacked controls to prevent manipulation, data deletion, and unauthorized access. For example, operators responsible for generating CGMP records had full administrator rights to access the computers containing temporary data prior to routine transfer of the data to a server. All analysts shared a common login ID and password. Your use of universal administrator privileges and a single common login/password meant that actions could not be traced to specific individuals. Additionally, because the audit trail feature on the system's software was not configured to create a file history for all activities executed by the user during analysis, your electronic data was exposed to manipulation and/or deletion without traceability.
8/4/2016	China	Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory	**3. Failure to record activities at the time they are performed.** During the inspection, our investigators observed **(b)(4)** different analysts pre-dating or backdating results in your API quality control laboratory. Analysts were observed using pre-dated laboratory worksheets to document system suitability testing for high performance liquid chromatography (HPLC) analyses for **(b)(4)** purity testing. The worksheets were dated five days before the tests that they purported to document were actually carried out. Our investigators also observed analysts signing and dating microbiological testing laboratory worksheets five days before the test results would be available and backdating laboratory worksheets for impurities and content testing by four days.
8/4/2016	China	Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory	Data Integrity Remediation Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing

			operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the analytical testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.
8/5/2016	US	Noven Pharmaceuticals	**1. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of test methods (21 CFR 211.165(e)).** During the inspection, we observed that your methods for measuring **(b)(4)** are not scientifically sound. **(b)(4)**, or movement of adhesive past the edges or through the slit in a release liner, is a quality concern in transdermal drug delivery systems (TDDS) such as Minivelle and Daytrana.

			Excessive **(b)(4)** can lead to product detachment, expose the drug to other people, and other safety issues. We are concerned that your unsound methods could be masking product failures. The complaint rate for Minivelle increased by 50 percent from your 2013 reporting period (October 2012 – September 2013) to your 2014 reporting period. However, you failed to determine why. The following examples illustrate deficiencies with your testing methods. a. Your qualitative **(b)(4)** method **(b)(4)** for Minivelle relies on an analyst's subjective visual interpretation. On June 24 during our inspection, your analyst demonstrated this method for us and concluded that there was no **(b)(4)**. However, we observed adhesive residue on the pouch and around the edge of the product which is indicative of **(b)(4)**. b. Also during our inspection on June 29, we observed an analyst test a sample from Minivelle lot **(b)(4)** using the quantitative **(b)(4)** method **(b)(4)**. To prepare the sample for this test, the analyst handled the sample repeatedly, possibly resulting in unintentional **(b)(4)** adhesive removal. We advised you at that time that excessive sample manipulation could affect the accuracy of the test. Your written responses state that you would assess the testing methods and product specifications for Minivelle by September 2015. You indicated that you would implement a new **(b)(4)** method for **(b)(4)** by **(b)(4)**. Your response is inadequate because you continued to use method **(b)(4)** and **(b)(4)** for release testing to analyze **(b)(4)** prior to implementation of a suitable method. c. During the inspection, we discovered that you still have not validated test method **(b)(4)** for **(b)(4)** of your Daytrana TDDS. The test method is intended to detect adhesive transfer from the TDDS to the removable release liner. When this adhesive transfer occurs, the drug is removed from the TDDS and thus the product is rendered unusable. From April 2014 to March 2015, 45 percent (1,734) of your firm's complaints for Daytrana were for tight release (hard-to-remove liners) and adhesive transfer that impeded users from removing the liner. You did not detect this problem during your quality control testing or when you tested samples from **(b)(4)** for stability monitoring. In your response you stated that you misplaced the method validation package and that you will attempt to locate the original at your off-site storage facility. You also stated that you will assess method **(b)(4)** to determine how it can be improved to reliably detect adhesive transfer.

			Your response is inadequate because you have not demonstrated that you validated method **(b)(4)** or that it can reliably detect adhesive transfer. In response to this letter, provide the following: • For distributed Minivelle and Daytrana lots that you tested with unsound methods, details of interim action you will take, including enhanced complaint monitoring and trending. Also specify other action you will take, such as notifying customers and recalling products if data indicate defective products are in the marketplace. • The timeframe by which you will submit your new **(b)(4)** method to the Agency for evaluation. • Your current version of method **(b)(4)** for testing Daytrana, the original validation package, and any revalidation that you have performed.
8/5/2016	US	Noven Pharmaceuticals	**2. Your firm failed to record and justify any deviations from required laboratory control mechanisms (21 CFR 211.160(a)).** On June 29, our investigator watched an analyst testing Minivelle lot **(b)(4)** for peel adhesion. The investigator observed that the analyst failed to follow your procedures. For example: a. The analyst aborted testing of two TDDS because the pulley detached from the TDDS during the peel test. The analyst tested two additional TDDS but did not document the aborted tests as required by your SOP (QC-0009). The analyst told our investigator that you record only completed tests. b. Our investigator also observed that your analyst did not adequately calibrate the adhesive testing machine used as required by your SOP (QC-0138). Specifically, the analyst failed to use the appropriate range of weights to bracket expected results for the TDDS. Using appropriate calibration weights is important for assuring accuracy over the range of expected test results. A review of the logbooks for the instrument since November 25, 2014, found that analysts always used weights that did not bracket the expected results. Therefore the adhesive tack testing results may not be accurate due to improper calibration of the instrument. In your response, you stated that you purchased a new calibrated digital level and that you will use a larger weight for the upper calibration limit. Your response is inadequate because you did not indicate whether you have retrained and recertified your technicians and analysts. You also did not indicate whether you are using an appropriate weight for the lower calibration limit in order to accurately detect adhesive failure below or at **(b)(4)**.

			In response to this letter, provide information about your calibration weight limit for the lower end of your test scale. Also provide details about your global corrective action and preventive action plan including remediation of laboratory procedures, methods, training and staffing improvements, and other appropriate steps.
8/5/2016	US	Noven Pharmaceuticals	**4. Your firm failed to maintain written records so that data therein could be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures (21 CFR 211.180(e)).** You failed to analyze product and process data for commercial batches of Minivelleto identify adverse trends. Our review of the stability summary data for the 15 lots of Minivelle produced in 2014 identified quality attributes that are inconsistent with the specifications in your approved new drug application for Minivelle (NDA 203752). For example: a. You manufactured commercial batches using the raw material silicone with significantly **(b)(4)** values than that used in clinical batches. You updated the **(b)(4)** specification in June 2014 due to **(b)(4)** failures of Minivelle lots **(b)(4)** and **(b)(4)**. However, the **(b)(4)** and adhesion data to support this change in specification was unreliable, and you continue to have **(b)(4)** failures. b. Probe tack tests found average adhesion of Minivelle commercial batches to be much higher than the values specified in your new drug application. Test results for your commercial batches were between **(b)(4)** and **(b)(4)** grams. The specification in your application is no less than **(b)(4)**, based on tack values between **(b)(4)** and **(b)(4)** grams for the clinical investigation and registration batches. Your firm failed to identify and investigate this shift in probe tack results. Your response stated that you will develop and validate a **(b)(4)** test method, develop specifications based on **(b)(4)**, and will initiate a change control to update your procedure. Your response is inadequate because you failed to provide sufficient details of your corrective action and preventive action plan. It is imperative that you fully understand your products and processes, in part, to ensure that variation in tack and other adhesion properties is detected and properly controlled to prevent unpredictable drug delivery. In response to this letter, provide the following: • A summary of your retrospective review of all drug products considering the new requirements in your revised **(b)(4)** product review procedure SOP-QA-0076. • A timeframe for submitting a **(b)(4)** supplement to **(b)(4)** with new specifications. These new specifications should be based on additional product and process knowledge, including a full

			understanding of your adhesive manufacturer's process capabilities and raw material properties (such as **(b)(4)** and **(b)(4)**) and the influence of these properties on finished product and other critical components.
8/10/2016	China	Hushou Aupower Sanitary Commodity Co Ltd	**5. Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced (21 CFR 211.188).**
8/11/2016	China	Zhejiang Hisoar Pharmaceutical Co	**1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your electronically-stored data and paper records. When you encountered suspect and out-of-specification (OOS) results, you retested samples until you obtained desirable results. You did not investigate, review, or report original results. You relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed to established specifications and standards. For example, during the inspection, we reviewed electronic data from your high performance liquid chromatography (HPLC) system. An unknown impurity peak was present when the original three-month stability sample of **(b)(4)** batch **(b)(4)** was run on October 9, 2014. This unknown peak was OOS and would have caused the sample to fail for unknown impurities, but it was not included in the official record for this stability test. Instead, an analyst ran a new sample to obtain a passing result on October 10, 2014, and only the passing result from the second sample was reported in the official record. In your response, you stated that the analyst thought that the unreported OOS value was related to the reference solution and not the sample being tested. You said the analyst was afraid of making mistakes, and invalidated the data without notifying management. You acknowledged that the data should not have been invalidated without an OOS investigation and committed to revise procedures.
8/11/2016	China	Zhejiang Hisoar Pharmaceutical Co	**2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.** During the inspection, we observed that your laboratory systems lacked access controls to prevent deletions or alterations to raw data. For example, our investigator reviewed the electronic folder containing data files generated when your firm tested(b)(4) batches

			of (b)(4) API for residual solvents by gas chromatography (GC). The investigator compared the file names in the folder with the metadata generated by the Chemstation software you used to operate your GC system, and found that two chromatograms had been deleted from the system. Because there were no controls restricting operators' or supervisors' abilities to alter or manipulate the data, an analyst had completed two runs and deleted the results, and then changed the subsequent file names in the folder where reported data was stored to make it appear that the deleted runs never occurred. In your response, you stated that two injections were deleted from the system because the analyst believed that an unstable baseline made retaining the files unnecessary. You also confirmed that your software had no access controls and that your analysts had authorization to delete data.
8/11/2016	China	Zhejiang Hisoar Pharmaceutical Co	**3. Failure to record activities at the time they are performed.** During the inspection, we observed that you did not have worksheets for recording microbial test results and that you failed to contemporaneously document microbial limits test results for (b)(4) API batch (b)(4). In your response, you stated that tests for microbial limits were not routine for (b)(4). The microbiologist documented test methods and results "when she had time," and "there was a possibility that our QC microbiologist documents results by memory instead of document (sic) at time of operation." Your response did not demonstrate the reliability of any data recorded and reported in the past. In your response to this letter, provide: • microbial limits retest data of all (b)(4) API batches within expiry • your review of all microbial test methods to verify suitability for intended use 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

			application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.
8/11/2016	China	Zhejiang Hisoar Pharmaceutical Co	**Delay producing records during inspection** Some records that our investigators requested during the inspection were not available for review. For example, during the inspection of the microbiology laboratory, our investigators requested the completed microbial QC worksheet for **(b)(4)** API batch **(b)(4)**. Your laboratory staff led our investigators out of the lab to another room where, according to your staff, the completed document was located. After approximately 30 minutes outside of the laboratory without being provided the completed worksheet, our investigators reentered the microbiology lab and observed a microbiologist with a partially-completed QC worksheet for the batch in question. Later, a member of your laboratory staff told our investigators that, contrary to initial statements, the "original" completed QC worksheet never existed. 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
8/11/2016	China	Zhejiang Hisoar Pharmaceutical Co	Data Integrity Remediation Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

			A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.

			• Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product,conducting additional testing, adding lots to your stability programs to assure stability, drug
8/12/2016	India (2)	Unimark Remedies Ltd	**2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.** Our inspection documented that you modified the manufacturing process multiple times for **(b)(4)** API. Your quality unit did not approve these changes, nor did you document them through a change control review process. Furthermore, you did not place samples from any of the batches produced through modified processes in your stability monitoring program to assess the effects of these changes on the quality of your API throughout the expiry period. In your response you referenced stability data from batches not manufactured using the modified processes discussed above. Your response is inadequate because you do not have stability data to demonstrate that your API meets specifications throughout its expiry period.
8/12/2016	India (2)	Unimark Remedies Ltd	**3. Failure to maintain training records of employees involved in the manufacture of intermediates or API.** Our investigator found that your employees' CGMP training records contained numerous discrepancies that raise doubts regarding their authenticity. For example, the inspection documented that 10 of 11 training records contained identical handwritten responses. Our investigator also found incomplete training assessment forms for two employees. The forms indicated that the employees had not been evaluated as required in your procedures, yet the employees' training files stated that they had been evaluated as "very good" for the skills in question. In response to this letter, provide a corrective action and preventive action plan to address your poor documentation practices and oversight of training activities. Include an updated training plan describing how you will ensure that all employees are adequately qualified to perform their assigned responsibilities in the manufacturing and laboratory operations.
8/12/2016	India (2)	Unimark Remedies Ltd	**1. Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.** Your firm routinely re-tested samples without documented justification and deleted analytical data.

			Our inspection found that you did not adequately investigate failing or atypical results. Although you obtained failing results in 2014, you did not initiate and document investigations for those failing results until July 2015. In addition, the conclusions of your investigations lacked supporting data. Your firm's response attributed all unauthorized retesting of API batches to the lack of adequate training of your analysts.
8/15/2016	US	Frontida	**1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products; and the authority to review production records to assure that no errors have occurred or, if errors have occurred, assure that they have been fully investigated. (21 CFR 211.22(a))** Significant findings indicate that your quality unit is not fully exercising its authority and responsibilities. We detail three examples below. Your firm must provide the quality unit with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality. *Release of potentially contaminated product* Your quality unit knowingly released 27 lots of various strengths of clonidine HCl tablets on or about March 5, 2015, despite evidence that active pharmaceutical ingredient (API) used in their manufacture (lot **(b)(4)**) was potentially contaminated. Your supplier recalled this lot of API based on **(b)(4)** inspectional findings that indicated inadequate controls to prevent cross contamination of the API. Your firm was notified of this recall as early as July 16, 2014. Based on your supplier's recall notice, your firm initially placed 27 lots of clonidine HCl tablets on hold starting on July 16, 2014. You then hired a contract testing laboratory to analyze retain samples of the clonidine API lot for cross contamination. However, your contract laboratory provided documentation that its test method was not validated to detect low levels of cross contamination, and explicitly stated that the test results "may not be used for batch release." Despite this, your firm released the 27 lots of clonidine HCl in March 2015 without testing your finished products using a method that was both validated and sufficiently sensitive to detect cross contamination. On July 9, 2015, during our inspection, your firm recalled all 27 lots. In your response you committed to engaging a third party to assess your supplier program to determine when you should take additional steps to assess your API supplier. *Inadequate investigation of stability failure*

			You did not adequately investigate the stability failure of lot **(b)(4)** of felodipine 2.5-mg tablets for an unknown impurity. The product specification for unknown impurities is **(b)(4)** percent, but your three-month stability test result for this lot was **(b)(4)** percent impurities. You opened an investigation into the stability failure on February 12, 2015. Your own records indicate that as of April 29, 2015, you were aware that benzophenone had leached into the tablets from the ink and varnish on the primary container label, but you did not recall this lot until July 16, 2015, during the FDA inspection. In your response, you committed to developing a method to quantify benzophenone in your products as well as a method to screen labels prior to use. *Discrepancies in CGMP-related records* Your quality unit failed to ensure that CGMP-related records are accurate, contain appropriate documentation, and are consistent with your standard operating procedures (SOP). We found multiple discrepancies in quality unit-approved records, such as: • investigation reports containing data and documentation from unrelated investigations • records signed with only a first name • records missing dates • illegible entries in logbooks and laboratory notebooks During the inspection, you attributed some of the documentation discrepancies to your practice of cutting and pasting between different investigation reports. You also committed to correcting other deficiencies.
8/15/2016	US	Frontida	In response to this letter: • Provide a plan to ensure that your quality unit will adequately exercise its authority and perform its responsibilities. • Describe how you ensure that your quality unit has rejected and will continue to reject all components and drug products that are not of adequate quality, purity, or safety. • Describe improvements to your supplier qualification and auditing program and specify how you ensure that oversight of suppliers is commensurate with risk to your finished products. • Provide the results of your audit of your clonidine HCl API supplier. • Conduct a retrospective evaluation of your drug products within expiry to ensure they do not exceed specifications for any known or unknown impurities. Provide the results of this evaluation

			and indicate the steps you have taken to investigate any OOS results you identify as part of this retrospective evaluation.
8/15/2016	US	Frontida	**Access to information during inspection** During the inspection, there were numerous instances where your firm failed to provide our investigators with information regarding investigations, corrective actions, and preventive actions in a manner that would allow the investigators to fully understand and evaluate your firm's internal processes and compliance with CGMP requirements. Your vice president of quality repeatedly denied any knowledge of your clonidine HCl API supplier's recall, even though e-mail evidence collected during the inspection showed that this individual had been notified of the recall as early as July 16, 2014. During the inspection, your firm removed this individual from his position. In your response, you stated, "Mutual recognizes that the manner in which it provided information about this issue to the investigators during the inspection did not effectively convey Mutual's process for product disposition or the rationale for its decisions throughout the handling of the batch of Clonidine HCl API." 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
8/25/2016	India	Pan Drugs Limited	1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in process materials, packaging material, labeling, and drug products (21 CFR 211.22(a)). Your firm's quality unit allowed the use of adulterated (b)(4) USP API, dated May 25–31, 2015, manufactured at the Pan Drugs Ltd. Nandesari facility. The Pan Drugs Ltd. Nandesari facility was placed on FDA import alert 66-40 on May 5, 2015, for egregious CGMP deviations. Your firm used this API for the manufacture of (b)(4), which were then shipped to the U.S. market from October 7 to November 23, 2015. Additionally, your quality unit approved certificates of analysis (COA) for (b)(4) and (b)(4) API, as well as finished products, prior to conducting all quality control and release testing. Your production manager falsified the documents by signing and dating the "Prepared By" and "Checked By" sections of the COA.

			Furthermore, your quality unit failed to identify data integrity issues in 11 batch production records reviewed by our investigator. Your production manager admitted that he falsified the signatures of other employees in the “Prepared By,” “Reviewed By,” “Approved By,” and “Authorized By” sections. According to your response, you recognized that these practices were not adequate. You intended to implement a signature list and revise your SOPs to address these failures. However, these actions do not address the quality unit failures observed.
8/25/2016	India	Pan Drugs Limited	4. 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)). For example, the computer in your quality unit area did not have controls to restrict access and prevent unauthorized changes to data files and folders. All employees had access to your Annual Product Review (APR) spreadsheet. The desktop computer containing the APR was not locked. In your response, you committed to “reassessing the GMP” requirements for computer-based systems; you stated the systems would be “evaluated, checked and validated.” You did not include a timeline or specify a plan to review released batches and determine the impact of the deficiency
8/25/2016	India	Pan Drugs Limited	Data Integrity Remediation Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.

			An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related data at your firm. Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. A status report for any of the above activities already underway or completed.
8/25/2016	Brazil	Lima & Pergher Industria e Comercio S/A	**4. Your firm failed to ensure that its drug product bore an expiration date that was supported by appropriate stability testing (21 CFR 211.137(a)).** Your firm had no stability data to support your expiration date.

8/25/2016	Brazil	Lima & Pergher Industria e Comercio S/A	**Data Integrity Remediation** Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations. C. A management strategy that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to the FDA. • A comprehensive description of the root cause of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting

			additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.
9/6/2016	China	Hebei Yuxing Bio-Engineering Co Ltd	1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards. Your quality control laboratory failed to record and maintain complete data from analyses of your (b)(4) ((b)(4)) API. For example: • Prior to conducting official analyses,your quality control laboratory performed “experimental” analyses on product batches to assess whether your API met specifications, but failed to document these “experimental” tests in official laboratory records or to justify their exclusion. Our investigator found the results of 2,404 high performance liquid chromatography (HPLC) injections in a folder titled “Experimental” on instrument SZG-002-006l. Your quality unit indicated that these “experimental” injections were being conducted in all (b)(4) chromatographic units in your quality control laboratory. Your management provided different explanations in an attempt to justify the practice, including “fear” that the sample results would not pass. • Our review of the audit trails of chromatographic systems SZG-002-009, -010, -011, and -012 documented that your laboratory analysts deleted raw chromatographic data on multiple occasions. Your firm indicated that analysts may have been testing the system and may have deleted associated files. You also indicated that the deleted files may represent aborted analyses. However, we documented that some audit trail entries of deleted raw data files contained batch numbers for actual batch samples being tested. There is no assurance that laboratory records and raw data are accurate and valid. We acknowledge your decision to revise your current procedure for the testing of (b)(4). In response to this letter, provide a summary of how your chromatography procedures will conform to U.S. Pharmacopeia requirements, including those for the establishment of system suitability. In addition to deciding to revise your (b)(4) testing procedure, in your response you commit to acquiring additional chromatographic instruments, restricting certain chromatographic instruments to specific analyses, installing a new data control system, upgrading instrument

			software, and enabling data integrity features included in the laboratory software. Your response is inadequate. None of your explanations justify your failure to maintain complete records, nor do they support your practice of substituting repeat tests after failing results. Acquiring new instruments, installing new and upgraded software, and enabling various features on software are only effective if you have implemented appropriate procedures and systems to ensure that your quality unit reviews all production and control data and associated audit trails as part of the batch release process.
9/12/2016	Brazil	Mappel Industria de Embalagens, SA	**Your firm failed to maintain production, control, or distribution records associated with a batch of a drug product for at least one year after the expiration date of the batch (21 CFR 211.180(a)).**
9/15/2016	Japan	Nippon Fine Chemical Co	Your firm limited an inspection and/or refused to permit the FDA inspection as follows: **1. Barring access to areas** During the inspection, your firm limited the investigator's access to the quality control laboratory. The quality control manager directed employees to stand shoulder-to-shoulder, barring our investigator from accessing portions of the laboratory and the equipment used to analyze drugs for U.S. distribution.
9/15/2016	Japan	Nippon Fine Chemical Co	Your firm limited an inspection and/or refused to permit the FDA inspection as follows: **2. Refusal to provide copies of documents** Your firm manufactures certain drugs for the Japanese and U.S. markets using the same equipment and processes, and divides lots for distribution between the two markets. During the inspection, our investigator reviewed complaints you received about your drugs from your customers, including complaints that your drugs contained glass, hair, cardboard, metal, product discoloration, and a black spider. Your firm limited the inspection by refusing to provide FDA copies of these records.
9/15/2016	Japan	Nippon Fine Chemical Co	Your firm limited an inspection and/or refused to permit the FDA inspection as follows: **3. Limiting photography** During the inspection, our investigator attempted to take pictures of the **(b)(4)** apparatus used to manufacture drugs for U.S. distribution. Your quality assurance manager impeded the inspection by preventing our investigator from photographing this piece of equipment.

9/6/2016	China	Hebei Yuxing Bio-Engineering Co Ltd	**1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** Your quality control laboratory failed to record and maintain complete data from analyses of your **(b)(4)** (**(b)(4)**) API. For example: rior to conducting official analyses,your quality control laboratory performed “experimental” analyses n product batches to assess whether your API met specifications, but failed to document these xperimental” tests in official laboratory records or to justify their exclusion. Our investigator found the esults of 2,404 high performance liquid chromatography (HPLC) injections in a folder titled Experimental” on instrument SZG-002-006l. Your quality unit indicated that these “experimental” jections were being conducted in all **(b)(4)** chromatographic units in your quality control laboratory. our management provided different explanations in an attempt to justify the practice, including “fear” hat the sample results would not pass.)ur review of the audit trails of chromatographic systems SZG-002-009, -010, -011, and -012 ocumented that your laboratory analysts deleted raw chromatographic data on multiple occasions. our firm indicated that analysts may have been testing the system and may have deleted associated les. You also indicated that the deleted files may represent aborted analyses. However, we ocumented that some audit trail entries of deleted raw data files contained batch numbers for actual atch samples being tested. There is no assurance that laboratory records and raw data are accurate nd valid. We acknowledge your decision to revise your current procedure for the testing of **(b)(4)**. In response to this letter, provide a summary of how your chromatography procedures will conform to U.S. Pharmacopeia requirements, including those for the establishment of system suitability. In addition to deciding to revise your **(b)(4)** testing procedure, in your response you commit to acquiring additional chromatographic instruments, restricting certain chromatographic instruments to specific analyses, installing a new data control system, upgrading instrument software, and enabling data integrity features included in the laboratory software. Your response is inadequate. None of your explanations justify your failure to maintain complete records, nor do they support your practice of substituting repeat tests after failing results. Acquiring new instruments, installing new and upgraded software, and enabling various features on software are only effective if you have implemented appropriate procedures and systems to ensure that your quality unit reviews all production and control data and associated audit trails as part of the batch release process.

9/6/2016	China	Hebei Yuxing Bio-Engineering Co Ltd	**2. Failure to follow and document laboratory controls at the time of performance, and failure to document and explain any departures from laboratory procedures.** During the inspection, your firm provided our investigator a chromatogram for an assay analysis of **(b)(4)** batch **(b)(4)** dated August 30, 2014, at 9:46:39 a.m. Your firm later submitted to FDA a different chromatogram corresponding to the same analysis, instrument, date, time, and batch. The second chromatogram appears exactly the same as the one provided during the inspection, but it includes a different method file name, column type and serial number, and system temperature. Both versions of these documents cannot represent the actual assay analysis that you conducted for batch **(b)(4)** on August 30, 2014, at 9:46:39 a.m.
9/6/2016	China	Hebei Yuxing Bio-Engineering Co Ltd	Data Integrity Remediation Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

			B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.
9/26/2016	Netherlands	Delarange Cosmetics and Healthcare BV	**2. Your firm failed to establish a quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products. (21 CFR 211.22(a))** You stated to our investigator that your firm does not have a quality unit to review and approve the release of your drugs.
9/29/2016	Switzerland	Laboratoire Sintyl S.A.	**1. You failed to establish written responsibilities and procedures applicable to the quality control unit, including the review of out-of-specification results and customer complaints.**

			(21 CFR 211.22(d)). During the inspection, you indicated that you have no independent quality unit.
9/29/2016	Switzerland	Laboratoire Sintyl S.A.	**2. Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).** During the inspection, you acknowledged that your firm did not test all batches of finished drug product prior to release. For example, in 2015 you tested only five of the **(b)(4)** batches shipped to the United States. We note you did not perform the active ingredient assay for batch #**(b)(4)** prior to release. FDA analysis showed this batch contained no active ingredient.
9/29/2016	China	Yangzhou Hengyuan Daily Chemical Plastic Co. Ltd.	**1. Your firm failed to provide adequate written production and control procedures which are designed to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess (21 CFR 211.101).** FDA collected samples of your **(b)(4)** batch #**(b)(4)** at the port of entry. FDA Laboratory analysis found that your **(b)(4)** did not contain any of the labeled active ingredient, **(b)(4)**. FDA denied entry of the shipment accordingly and notified your customer, **(b)(4)**, which filed a complaint with you. Your subsequent investigation into the customer complaint for batch #**(b)(4)** revealed that, during **(b)(4)** of components, you added the wrong ingredient, **(b)(4)**, instead of the active ingredient.
10/13/2016	Hungary	Teva Pharmaceutical Works Private Limited Company	6. 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)) Your stand-alone computer systems lacked controls, such as routine audit trail review and full data retention, to prevent analysts from deleting data. Although you implemented a procedure to begin reviewing audit trails of your high-performance liquid chromatography (HPLC) Empower system on January 11, 2016, you had not performed any reviews prior to our inspection. Furthermore, the procedure you implemented on January 11 required (b)(4) random audit trail review (b)(4). We acknowledge your commitment to strengthening your procedures to assure user access restrictions and implement audit trails for computerized systems. However, simply activating audit

			trail functions and instituting user controls are insufficient to correct the data integrity problems observed at your facility and to prevent their recurrence. In response to this letter, provide details of your retrospective review of the HPLC and other laboratory data, such as Fourier transform infrared spectroscopy, gas chromatography, UV spectrophotometry, and (b)(4) analyzer data. Indicate the period covered in your review and your rationale for selecting that timeframe.
10/13/2016	Hungary	Teva Pharmaceutical Works Private Limited Company	**7. Your firm failed to follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch. (21 CFR 211.186(a))** Our investigators found quality-related documents in a waste bin. Among these documents were an incomplete sterility test data sheet, a form used to track the movement of **(b)(4)** samples, a media fill incubation card, and others. The incomplete sterility test data sheet had been filled out to track information about a "**(b)(4)**" sterility check. After an error was observed on the original data sheet, the record was torn and discarded with no written explanation.
10/13/2016	Hungary	Teva Pharmaceutical Works Private Limited Company	**Data Integrity Remediation** Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies and record retention policies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.

			• A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies, including but not limited to investigation into your laboratory testing raw data, reported results, and quality oversight for all products and process lines. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. Provide a detailed report from your consultant. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data (both microbiology and chemistry), manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (for example, training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.
10/18/2016	Czech Republic	Interpharm Praha A.S.	**1. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.** Your quality control unit did not have basic controls to prevent changes to your electronically-stored laboratory data. Your analysts had user privileges to the Empower-2 system used to generate and

			analyze chromatographic data that allowed them to eliminate failing, atypical and satisfactory results with no notification; alter peak areas; and add or eliminate samples from sequences without authorization. During the inspection, we reviewed an audit trail from your Empower-2 system that stored 8,906 entries. Of these, well over half indicated some form of data deletion or manipulation, including at least 1,441 instances of deleted results, at least 3,643 instances of manual integration, and at least 194 instances of altered running sample sets. Your personnel confirmed that these actions are common during chromatographic data processing. We found that you did not have a procedure in place to indicate the requirements and level of restrictions for users of the automated system. Your quality unit must review all pertinent analytical data when making batch release decisions. However, your automated system permitted analysts to delete and alter test results without authorization. As a result, your quality unit was presented with incomplete and inaccurate information about the quality of your drugs. According to your response, you restricted access and permissions in the Empower 2 automated data system. However, your response does not demonstrate how the specific controls you have implemented prevent deletion or alteration of data, nor have you shown how you will ensure that these permissions are documented, implemented, and followed. Finally, you have not shown how these controls ensure that records relied upon for batch release and other quality review decisions are complete and accurate.
10/18/2016	Czech Republic	Interpharm Praha A.S.	**1. 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)).** For example, our investigator reviewed an audit trail for impurities testing conducted on **(b)(4)** validation lot **(b)(4)**, number **(b)(4)** vial # **(b)(4)**, Injections 1 and 2. The audit trail revealed many deleted results and manual integrations. As discussed above, deleted and altered analytical test results mean that your quality unit is presented with incomplete and inaccurate information about the quality of your drugs.
10/18/2016	Czech Republic	Interpharm Praha A.S.	Data Integrity Remediation Your quality system does not adequately ensure the adequacy and integrity of data to support the safety, effectiveness, and quality of drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

			In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data, records, and reporting. Your investigation should include: - A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and justification for any part of your operation that you propose to exclude. - Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. - An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of your data integrity deficiencies. • We recommend that a qualified third party with specific expertise in the area where potential lapses were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effect of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations. C. A management strategy that includes the details of your global corrective action and preventive action plan. Your strategy should include: • The detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to the FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses

			remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your data. • A status report for any of the above activities already underway or completed.
10/19/2016	China	Beijing Taiyang Pharmaceutical Industry Co Ltd	**1. Your firm delayed, denied, or limited an inspection, or refused to permit the FDA inspection.** On November 16, 2015, our investigators observed through a window a warehouse containing numerous drums bearing your company's label. When our investigators requested access to this warehouse, you barred them from entering the warehouse to examine the containers or the material in them without giving a reasonable explanation. The following day, you gave our investigators access to the warehouse. However, upon entry they observed that a significant number of drums had been removed and were not available for inspection. When they asked about the drums they had observed the previous day, you provided no explanation of the whereabouts or contents of the drums. You delayed FDA's access to the warehouse and limited FDA's inspection by removing the drums before our investigators could inspect them.
10/19/2016	China	Beijing Taiyang Pharmaceutical Industry Co Ltd	**2. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** Our investigators observed systemic data manipulation across your facility. They documented unexplained deletions of laboratory test results. They discovered that you repeated tests until you obtained acceptable results and that you failed to investigate out-of-specification or otherwise undesirable test results. Your firm relied on these falsified and manipulated test results to support batch release and stability data. Your firm routinely re-tested high performance liquid chromatography (HPLC) samples and deleted previous chromatograms without justification. Your management acknowledged that employees in your quality control laboratory have access,

			authority, and the ability to delete and repeat HPLC injections when undesirable results were encountered prior to reporting final results. Your response states repeated testing was due to quality control operators continuously injecting solvents until a stable baseline was achieved. The response also states the results of repeated tests were deleted to decrease the number of saved chromatograms on your hard drives. Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes. In order to exclude data from the release criteria decision-making process, you must have valid, documented, scientific justification for its exclusion. Reducing the number of records on your hard drives is not a sufficient justification for excluding data. Your response is inadequate because you have not shown how you will correct the data manipulation and falsification practices discussed above, nor have you demonstrated how you will ensure that all CGMP test results are retained and considered by your quality unit as a part of batch release.
10/19/2016	China	Beijing Taiyang Pharmaceutical Industry Co Ltd	**3. Failure to ensure that all quality-related activities are recorded at the time they are performed.** In the production area, our investigators witnessed an employee backdating production batch records for seven batches of **(b)(4)** (batches **(b)(4)** to **(b)(4)**) and transcribing data from a master template record. Furthermore, analysis of the transcribed data for these seven **(b)(4)** batches and for approximately 40 batches of **(b)(4)** API, indicated that you did not record data contemporaneously and that missing data was later falsified so the official records would appear complete. In the laboratory area, our investigators observed a laboratory analyst attempting to remove a large pile of loose documentation from the HPLC instrumentation room. Upon reviewing the pile of documents, investigators found a significant number of partially completed quality control data worksheets and scratch-paper records containing sample weight values. Our investigators compared these to the official quality control data worksheets and found numerous discrepancies in weights and calculations. Your response indicates that prior to this inspection you were operating without any document controls. You state that you revised procedures to ensure that distribution of all blank batch records and quality control documents would be done by the quality unit, and that controlled documents would now be identified with a “blue stamp.” However, unless the quality unit controls it by appropriate pagination and reconciliation or other appropriate means, a stamp system is insufficient to ensure that data is recorded contemporaneously. Your response also fails to investigate quality

			control worksheet and production batch record discrepancies to determine whether the data you relied on for drug release decisions was accurate.
10/19/2016	China	Beijing Taiyang Pharmaceutical Industry Co Ltd	**4. Failure to maintain batch production and laboratory control records to determine compliance with established API specifications before a batch is released or distributed.** On November 16, 2015, you told our investigators that you had stopped manufacturing **(b)(4)** API in September 2015. However, during our inspection, our investigators reviewed HPLC and gas chromatogram electronic audit trails that indicated you conducted multiple HPLC and GC analyses on **(b)(4)** batches of **(b)(4)** API from November 5 to 6, 2015 (batch numbers **(b)(4)** to **(b)(4)**). By your batch numbering system, these batch numbers correspond to batches manufactured in November 2015, two months past the date that you said you ceased production. During the inspection, you could not provide batch production records for these batches, nor did your instrument-use logbooks reflect the testing of these batches. Furthermore, the assay and related substance injection results for these **(b)(4)** batches had been deleted, according to your laboratory analyst, and could not be produced for review during the inspection. Your response reiterates that your company did not manufacture **(b)(4)** API batches with batch numbers of **(b)(4)** through **(b)(4)** and the test results that our investigators reviewed and asked about during the inspections were from old samples and tests performed for training purposes. Your response is inadequate because you did not explain how analyses for non-existent batches could be labeled with official unique batch numbers, nor did you explain how your laboratory control system permits the exclusion of analytical results, whether for training or other reasons, without justification.
10/19/2016	China	Beijing Taiyang Pharmaceutical Industry Co Ltd	Data Integrity Remediation Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your

			operation that you propose to exclude. Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. A status report for any of the above activities already underway or completed.
11/8/2016	Japan	Sekisui Medical Co., Ltd	2. Failure to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data. Our investigator observed that your laboratory systems lacked controls to prevent deletion of and alterations to electronic raw data. You do not have adequate controls for seven of (b)(4) high

			performance liquid chromatography (HPLC) systems and one of (b)(4) gas chromatography systems. For example, the audit trail on HPLC 15 did not record the (b)(4) batch (b)(4) assay. Your records indicate that the assay was performed on March 3, 2014, but your audit trail shows no assays performed between February 28 and March 4, 2014. Moreover, your analyst demonstrated to our investigator that he could change the data, including injection time and date, without the changes being captured in the audit trail, prior to printing the results. We acknowledge that you have committed to upgrading your analytical systems to be compliant with CGMP requirements. However, procuring new instruments, installing new and upgraded data acquisition software, and enabling various features on software are not sufficient alone. These steps will be effective only if you implement appropriate procedures and systems to ensure that your quality unit reviews ll production and control data and associated audit trails as part of the batch release process.
11/8/2016	Japan	Sekisui Medical Co., Ltd	**1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established API specifications and standards.** Our investigator found that you failed to maintain complete data from all laboratory analyses, and that you relied on the incomplete information to determine whether your drugs met established specifications. For example: a. Numerous data files were found in the recycle bin folder on the computer connected to gas chromatography instruments GC-4 and GC-6. Specifically, our investigator found deleted data for residual solvent testing for **(b)(4)** lot **(b)(4)** in the recycle bin. Your records show that you retested the lot without documented justification or an investigation. You retained only the final test result. b. During the inspection our investigator requested residual solvent release test data for two of your API, **(b)(4)** and **(b)(4)**. You were unable to retrieve this data. Any data created as part of a CGMP record must be retained so that it can be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes. We acknowledge that you commit to revising your SOP for archiving data. Your response is inadequate because it does not explain your failure to maintain complete records prior to the inspection. You also did not address validation of the systems you use to archive your data.

11/8/2016	Japan	Sekisui Medical Co., Ltd	**Data Integrity Remediation** Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: • A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.

			• Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.
11/8/2016	India	Srikem Laboratories	**1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** The audit trail for High Performance Liquid Chromatography (HPLC) instrument QCIEQPI40 showed multiple integrations conducted on the 18-month stability tests for unknown impurity content for **(b)(4)**, USP lots **(b)(4)**, without appropriate documentation, justification, and investigation. Your quality assurance manager agreed that these integrations were inappropriate. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, the results were out-of-specification for unknown impurity content. Your quality unit must review all pertinent analytical data when making batch release decisions in order to determine batch quality. In your response, you provided passing 24-month stability results for **(b)(4)** lots **(b)(4)**, and committed to use the auto integration function. Your response is inadequate because it does not address the failing 18-month stability results for these lots and does not demonstrate how you will ensure that you retain complete and accurate records of all tests.
11/8/2016	India	Srikem Laboratories	**2. Failure to follow and document laboratory controls at the time of performance.** Our investigator observed inconsistently-dated laboratory records. For example, your executed protocol records show that a 24-month time-point stability testing sample of **(b)(4)**, USP batch **(b)(4)**, entered the laboratory on February 14, 2015. Our investigator requested the HPLC data. You provided our investigator HPLC chromatogram printouts showing that the sample was tested on February 12 and 13, 2015: one or two days before your protocol shows that the samples even entered the lab. You were unable to find any raw data corresponding to these tests. The use-log of the HPLC does not contain entries for these runs. In another example, a printed chromatogram from related substance analysis performed by gas chromatography for **(b)(4)**, batch **(b)(4)**, was dated August 26, 2014. The data saved to your computer system from this analysis was dated December 28, 2013: nearly eight months before the date on the printed chromatogram.

			In your response, you attributed data discrepancies to software malfunctions, power outages, and personnel shift changes. Your response is inadequate because you have not sufficiently explained how you are improving controls, notwithstanding these claimed sources of discrepancies, to ensure the reliability and accuracy of the data you rely on to evaluate the quality of your drugs.
11/8/2016	India	Srikem Laboratories	Data Integrity Remediation Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following. A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations. C. A management strategy that includes the details of your global corrective action and preventive action plan. Your strategy should include: A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to the FDA. A comprehensive description of the root cause of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation

			and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. A status report for any of the above activities already underway or completed.
11/10/2016	China	Dongying Taindong Pharmaceutical Co Ltd	**1. Failure to adequately investigate and document out-of-specification results according to a procedure, and implement appropriate corrective actions.** Our investigator found that your firm repeatedly, and without justification, resampled and retested crude heparin batches when your quantitative polymerase chain reaction (Q-PCR) test for ruminant DNA exceeded your established specification limit of ≤ **(b)(4)** parts per million (ppm). As a result, your firm used crude heparin batches that potentially were out-of-specification (OOS) to manufacture heparin sodium API for the U.S. market.
11/10/2016	China	Dongying Taindong Pharmaceutical Co Ltd	**4. Failure of the quality unit to ensure that all critical deviations are investigated and resolved.** During the inspection, our investigator reviewed the high pressure liquid chromatography (HPLC) assay of over-sulfated chondroitin sulfate (OSCS) for crude heparin batches Y102-1404007, Y102-1404008, Y102-1404009, Y102-1404010, Y102-1404011, and Y102-1404012. The investigator found that the heparin standard and system suitability tests were run in isolation, rather than contemporaneously, approximately10 hours after the initial assay was completed. One of your employees explained that the analyst discovered that the system suitability sequence failed during the initial sample sequence. Instead of invalidating the associated sample results, the analyst reran the system suitability sequence with the heparin standard and the OSCS control. Passing system suitability testing indicates that requirements for precision are satisfied and HPLC functions appropriately: in this case, detecting the contaminant OSCS in heparin. The failure of your HPLC system suitability testing calls the validity of OSCS testing performed on the same equipment into question.

			We acknowledge that your SOP *Abnormal Incidents in the QC Lab*, which you provided with your response, establishes procedures for handling OOS incidents in the future. In response to this letter, provide the results of your retrospective review of all HPLC results for OSCS. Your review should demonstrate that: • your test results are accurate • you document and investigate interrupted HPLC runs • you perform passing system suitability results in the same sequence as the evaluated samples
12/8/2016	China	Baoying Couonty Fukang Medical Appliance Co., Ltd	**1. Your firm delayed, denied, or limited an inspection, or refused to permit the FDA inspection.** On June 6, 2016, during the inspectional walk through of the laboratory testing area of your facility, our investigator asked you to explain the microbiological testing processes used on the **(b)(4)** that you manufacture and distribute to the United States. Your firm's representative stated he would not disclose the firm's trade secrets. Our investigator explained that as part of the inspection, FDA needs to know the details of the operations, and that FDA does not disclose details of the information. Nonetheless, without reasonable explanation, the full test procedure was never provided. Your firm limited the inspection by refusing to disclose the manufacturing process you use in your facility to conduct microbiological testing on **(b)(4)**. You may wish to review FDA's guidance document, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection,* at http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm360484.pdf
12/8/2016	China	Baoying Couonty Fukang Medical Appliance Co., Ltd	**6. Your firm failed to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures. (21 CFR 211.80(a))** Specifically, your firm receives drums of **(b)(4)** raw material from your supplier without any identifying labels. Your firm does not perform identity testing or any other analysis onincoming raw materials upon receipt or prior to use, and you have no procedure that permits you to trace the source of the **(b)(4)** in each batch of finished products.
12/8/2016	Brazil	Antibioticos Do Brasil Ltda	**3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. (21 CFR 211.42(c)(10)(iv)).**

			You failed to adequately document environmental monitoring. For example, your records did not establish that during manufacture of **(b)(4)** lot **(b)(4)**, you collected environmental monitoring samples from all locations designated in your environmental monitoring procedure. Records did not clearly reconcile samples you collected with the results you obtained. Also, your procedure instructed operators to record environmental monitoring data only in instances where there are "any results different from zero." Your environmental monitoring records do not document any zero counts.
12/15/2016	Spain	Natura Bisse International S.A.	**3. Your firm failed to follow required laboratory control mechanisms, including any changes made to them, which were drafted by the appropriate organizational unit and reviewed and approved by the quality control unit (21 CFR 211.160(a)).** Your laboratory lacks appropriate controls over laboratory log sheets recording microbiology, physico-chemical and organoleptic test results. In your February 19, 2016, response, you stated that you amended your SOP PR-33 *Documentation Management* to require that log sheets and logbooks are to be controlled, reviewed, and approved by appropriate quality unit personnel. Your response is inadequate because it did not include a copy of the SOP or sufficient details regarding your proposed changes. In response to this letter, include your revised SOP PR-33. Also provide your investigation into how the uncontrolled documents may have affected the quality of your products, and your proposed corrective actions.
12/23/2016	India	Wockhardt Limited	3. 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)). While reviewing gas chromatography data on instrument QA/G07, our investigator found unreported results, including an out-of-specification (OOS) test result for raw materials. You did not investigate this OOS result or explain why you excluded the failing result from the official record. Our investigator also found that you reported only two of three chromatographic injections of sterile (b)(4) batch (b)(4) during in-process (b)(4) sample testing for residual solvent. You did not explain why you excluded the third injection. You decommissioned this instrument in July 2014 without reviewing the instrument data.

			Your response indicates that you have initiated a retrospective review of high performance liquid chromatography (HPLC) and gas chromatography (GC) data over a multi-year period. Your response is inadequate because it does not explain the depth of your electronic data review, or commit to a comprehensive retrospective review of raw data from all laboratory equipment and systems. In response to this letter, include a detailed update of the HPLC and GC electronic chromatographic data review. Include the total number of injections during the period, the number that your retrospective audit examined, and all anomalies and deviations observed. Specify the date of the test, products involved, all relevant results obtained, and batch (or other purpose) for which the testing was done. See Data Integrity Remediation caption below for our full request, including a determination of whether the data may have been associated with any drug applications.
12/23/2016	India	Wockhardt Limited	**4. 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)).** Our investigator found that you have not validated 12 computerized systems in your quality control laboratory. These systems are used for your stability chambers, ultraviolet (UV) and infrared (IR) spectrophotometers, and for thin layer chromatography (TLC). We acknowledge your commitment to validate your computerized systems. However, your response is inadequate. In response to this letter, include your assessment of the data generated from these stability chambers, UV and IR spectrophotometers, and TLC equipment.
12/23/2016	India	Wockhardt Limited	**5. Failure to record activities at the time they are performed, and destruction of original records.** *Data Recorded in Personal Diaries (Unofficial Notebooks)* In your process development laboratory, our investigator found several unofficial notebooks recording sample preparation for OOS investigations, route-of-synthesis experiments, and scale-up data. Our investigator found discrepancies between these unofficial notebooks and the official data retained by your quality unit. *Destruction of CGMP Documentation*

			CGMP documentation was discarded without being assessed by your quality unit. Our investigator found torn and shredded equipment maintenance documents, raw material labels, and change control work orders in your scrap yard awaiting incineration. Your staff lacked knowledge of your corporate procedure for the destruction and incineration of documents. In your response, you indicate that you have implemented corporate procedure CQA/021 to address the destruction of uncontrolled and controlled documents, and that you have retrained your employees. Your response is inadequate because you did not assess how your document-control practices affected your distributed products.
12/23/2016	India	Wockhardt Limited	Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. **In response to this letter, provide the following.** A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: • A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude. • Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party. • An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses. • A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified should evaluate all data integrity lapses. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations. C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

			• A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA. • A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm. • Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring. • Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data. • A status report for any of the above activities already underway or completed.

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